Acute presentation of a pituitary adenoma

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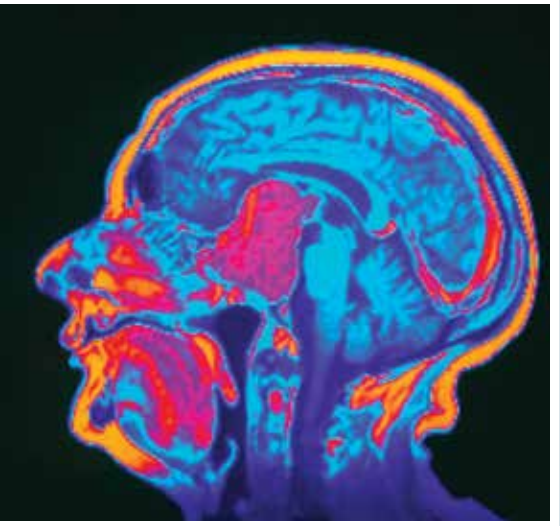
The immediate management and investigation of an acute endocrine presentation in general practice is discussed in this section. It is inspired by, but not based on, a real patient situation.



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John, a 68-year-old Caucasian man, is a new patient to your practice and has recently moved into the area. He presents to you complaining of a one-month history of nonspecific symptoms including lethargy, reduced appetite and low libido. Four weeks ago, he experienced a severe headache affecting his frontal region, which was associated with vomiting. This headache episode lasted three days and was not associated with any antecedent trauma or localising neurological deficit. He did not seek medical attention at the time and attributed his symptoms to the recent stress of moving. More recently, he has experienced occasional postural dizziness, particularly on standing quickly and on rising each morning.

His past medical history includes transient ischaemic attacks and significant cardiovascular risk factors including hypertension and dyslipidaemia. Interestingly, John stopped taking his dual antihypertensive therapy a couple of weeks ago due to the new onset of postural dizziness and reports that this improved his dizziness somewhat. He currently takes atorvastatin and aspirin.

John has a maternal family history of scleroderma and has a twin sister who suffers from multiple sclerosis. He lives with his wife and maintains an active lifestyle. They recently moved into the area from the country to be closer to their children. He has never smoked and drinks only occasionally.

What is your initial impression?

Answer: John's symptoms are nonspecific and potential differential diagnoses at this stage are broad. Red flags include his recent history of weight loss and anorexia, which raises suspicion of malignancy, and the transient but severe episode of headache that may provide a clue to possible underlying diagnoses. His postural symptoms that led him to cease long-term antihypertensive therapy suggest relative hypotension and raise the possibility of cardiac causes such as heart failure, autonomic instability or subacute infective endocarditis. Other chronic infections could be considered, for example, tuberculosis, and a travel history should be elicited.

Given John's family history, autoimmune disease is a possibility, although his age may render this less likely for a first presentation. Neurological, endocrine or renal diseases are also possible. With regard to endocrine causes, uncontrolled or longstanding diabetes mellitus could produce such symptoms, owing to sustained hyperglycaemia with osmotic diuresis and/or autonomic neuropathy; however, the absence of polyuria, polydipsia, nocturia and a history of diabetes makes this unlikely. A thyroid disorder (e.g. hyperthyroidism) is a possible diagnosis and should be explored. Pituitary or adrenal disease with glucocorticoid deficiency might also explain his symptoms. His decreased libido raises the possibility of concomitant androgen deficiency, suggesting a pituitary origin for his problems. This latter differential diagnosis is further supported by his recent episode of headache. This should be further investigated.

How do you examine John?

Answer: Given the generality of John's symptoms, a thorough physical examination is necessary.

On examination, John's blood pressure is 120/90 mmHg when lying down; however, this drops to 100/70 mmHg within 30 seconds of standing and John reports feeling dizzy. His jugular venous pressure is not raised. His heart sounds are dual, without any murmurs. There is

no peripheral oedema and there are no stigmata of infective endocarditis. His lung fields are clear to auscultation. His abdomen is soft and nontender, without palpable masses or organomegaly. There is no palpable lymphadenopathy and no goitre. Results of a neurological examination including visual field testing and checking extraocular movements are normal. John's reflexes are normal and examination of his skin reveals normal pigmentation with no rashes or lesions. He has a normal male pattern of hair growth and examination of his genitalia reveals normal testicular size bilaterally.

How do the examination findings direct your differential diagnoses and what investigations would you consequently like to perform?

Answer: Postural hypotension is typically caused by medications such as antihypertensive agents, alpha blockers, diuretics, tricyclic antidepressants and dopamine agonists. John does not take any of these medications, having recently ceased his blood pressure therapy. Abnormalities associated with autonomic dysfunction, such as diabetes mellitus, Parkinson's disease and Lewy body dementia, may cause postural hypotension of varying severity. However, John's symptoms and neurological examination do not support any of these diagnoses. Importantly, adrenal insufficiency, either primary or secondary, can result in orthostatic hypotension and should be considered in patients who present with a similar constellation of nonspecific symptoms without an obvious identifiable cause.

Given John's concerning history of headache, urgent MRI of the brain and blood tests are performed and John is referred to the hospital for urgent review. John's initial blood test results are shown in Table 1.

Table 1. Initial blood test results

Test	Result	Reference range
Sodium (mmol/L)	130	135–145
Potassium (mmol/L)	4.7	3.5–5.0
Chloride (mmol/L)	106	95–110
Bicarbonate (mmol/L)	23	22–32
Urea (mmol/L)	4.7	3.0–7.5
Creatinine (µmol/L)	65	60–110
eGFR (mL/min/1.73 m^2)	>90	>90
Corrected calcium (mmol/L)	2.42	2.15–2.55
Phosphate (mmol/L)	1.08	0.75–1.50
Magnesium (mmol/L)	0.73	0.7–1.10
Albumin (g/L)	39	35–50
Haemoglobin (g/L)	135	130–180
White cell count (× 10^9/L)	5.5	3.7–9.5
Platelets (× 10^9/L)	240	150–400
Thyroid stimulating hormone (mIU/L)	0.6	0.5–4.0
Free thyroxine (T_4) (pmol/L)	6.9	10–20
Free triiodothyronine (T_3) (pmol/L)	3.2	3.2–6.3
Follicle stimulating hormone (mIU/mL)	2.6	<9
Luteinising hormone (mIU/mL)	2.4	<9
Total testosterone (nmol/L)	4.1	9.5–28
Blood glucose (random) (mmol/L)	4.1	3.5–5.5

What are the most striking results of the initial blood tests?

Answer: The presence of hyponatraemia raises the possibility of cortisol deficiency, particularly in the context of relative hypotension. Furthermore, there is now biochemical evidence of secondary thyroidal and gonadal axis involvement (low free thyroxine [T_4] level, low total testosterone level and inappropriately low-normal thyroid stimulating hormone [TSH] and luteinising hormone [LH] levels). Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is also a differential diagnosis for patients with hyponatraemia; however, in the context of other pituitary axial involvement and John's previous headache, the possibility of a pituitary aetiology increasingly seems likely.

The results of the MRI brain are available and are reviewed by emergency department staff. The scan shows pituitary enlargement, 20 x 19 x 16 mm, with enhancement in the caudal right aspect of the pituitary gland, suggesting a pituitary adenoma. There was slight suprasellar extension, touching but not compressing the optic chiasm. A hyperintense T1 signal was noted, suggesting recent haemorrhage in this lesion.

What is the best investigation to do next?

Answer: On the basis of the MRI brain findings, 8:00 am (baseline) cortisol and adrenocorticotrophic hormone (ACTH) tests are ordered.

The results show John's levels are: cortisol, 41 nmol/L (reference range [RR], 275 to 555 nmol/L); ACTH, <1.1 pmol/L (RR, 2.2 to 13.3 pmol/L); insulin-like growth factor-1 (IGF-1), 12 nmol/L (8 to 24 nmol/L); and prolactin, 686 IU/mL (40 to 450 IU/mL).

In summary, John has evidence of a pituitary adenoma, with increased T1 signal on MRI suggesting recent haemorrhage. Furthermore,

he has evidence of secondary adrenal insufficiency, with low ACTH level and low morning cortisol levels, and symptomatic postural hypotension and hyponatraemia. He also has biochemical and clinical evidence of secondary hypothyroidism and secondary hypogonadism. His IGF-1 level is in the low-normal range. His prolactin level is mildly elevated due to stalk compression. Given these findings, John is diagnosed with a nonfunctioning pituitary adenoma with recent pituitary apoplexy and hypopituitarism of his cortisol, thyroid and gonadal axes.

What is pituitary apoplexy?

Answer: Classical pituitary apoplexy refers to sudden haemorrhage or infarction of the pituitary leading to its failure to secrete hormones. It is characterised by a clinical syndrome of sudden onset of headache and vomiting which, if severe, can be associated with visual impairment, ocular cranial neuropathies, diplopia and a decreased level of consciousness. It usually occurs in patients with a pre-existing nonfunctioning pituitary adenoma and evolves within hours to days. The size of the adenoma is important as there is a greater risk of apoplexy associated with macroadenomas than microadenomas.

Subacute pituitary apoplexy refers to asymptomatic pituitary haemorrhage or infarction and often presents insidiously. The timing of presentation is related to the extent of haemorrhage, oedema and tissue necrosis. It is a rare emergency that usually presents in the fifth or sixth decade of life, with a slight preponderance in men (1.6:1.0).[1] As there is often clinical unawareness of the pre-existing adenoma, the diagnosis is frequently delayed, with wide differential diagnoses. As such, a high degree of clinical suspicion is required.

The headache is typically retro-orbital, but can be bifrontal or diffuse. Lateral compression can affect the contents of the cavernous sinus leading to ocular palsies (most commonly third cranial nerve palsies) in up to 70% of patients. Decreased visual acuity and visual field defects (specifically, bitemporal hemianopia) are commonly seen and are caused by upward extension of the intrasellar contents, leading to compression of the optic chiasm.

John had no obvious precipitant to his presentation. Is this common?

Answer: In more than 60 to 80% of cases, pituitary apoplexy occurs spontaneously in previously asymptomatic patients and in those not known to have pituitary adenomas. Hypertension is the most common predisposing factor, seen in 26% of cases. Major surgery, especially coronary artery bypass grafting, can precipitate apoplexy. Anticoagulant therapy, coagulopathies, initiation of dopamine receptor agonist therapy, oestrogen therapy, radiation therapy and head trauma have also been shown to cause this abnormality.[2] Pregnancy and especially the postpartum period are also times that require a high index of suspicion for pituitary problems. Sheehan's syndrome (postpartum hypopituitarism) occurs as a result of ischaemic pituitary necrosis due to severe postpartum haemorrhage and can lead to the abrupt onset of hypopituitarism. Enlargement of the pituitary gland, small sella size, disseminated intravascular coagulation, type 1 diabetes and autoimmunity may all play a role in the pathogenesis.

Less commonly, dynamic testing of pituitary function using gonadotrophin-releasing hormone, thyrotrophin-releasing hormone, corticotrophin-releasing hormone or insulin tolerance testing have been reported to trigger pituitary apoplexy. Vigilance is therefore required in patients with known macroadenomas in any of these circumstances.

John had deficiencies of thyroidal, adrenal and gonadal axes of the pituitary at presentation. Is this typical?

Answer: Nearly 80% of patients with pituitary apoplexy have deficiency of one or more of the anterior pituitary hormones at presentation.[1] As most patients have an underlying macroadenoma, partial hypopituitarism would be expected to have been present even before the apoplectic episode.

The most clinically important deficit is the low ACTH level because it leads to acute corticosteroid insufficiency. This is especially dangerous at times of severe physical stress. Undiagnosed patients can be subjected to physiologically stressful investigation, for example gastroscopy for nausea and weight loss, leading to exacerbation of their underlying condition.

Hypothyroidism caused by TSH deficiency is also commonly seen. Gonadotrophin deficiency is seen in up to 75% of cases. Clinically significant posterior pituitary neurohypophyseal dysfunction is rare. The observed hyponatraemia is most commonly caused by hypocortisolaemia, rather than the syndrome of inappropriate antidiuretic hormone secretion. Prolactin may be low, normal, or mildly elevated as in John's case, owing to pituitary stalk compression and interruption of dopaminergic inhibition of anterior pituitary lactotroph cells.

The spectrum and severity of deficiency is compounded by the variation between time of symptom onset and the biochemical assessment of the pituitary. Pituitary function can deteriorate over time.

Could John have undergone a CT brain scan instead of MRI of the pituitary?

Answer: MRI is the radiological investigation of choice and has been found to confirm the diagnosis of pituitary apoplexy in over 90% of patients. However, CT is the most commonly used imaging modality in an acute clinical setting as it may be more readily available. CT scanning has been shown to be diagnostic in only 21 to 28% of cases, although a sellar mass was shown in up to 80% of patients.[1] Within the first three days after haemorrhage, intrasellar hyperdensity is seen on a noncontrast CT brain scan. This may be diffuse, local or multifocal within the gland. Unenhanced CT is sensitive to these changes but not specific.

Diagnostic difficulty may arise in distinguishing aneurysms from haemorrhage. MRI and MR angiography can aid in making this distinction. CT is less specific when performed during the subacute or chronic stages of gland haemorrhage when the appearance can be confused with cystic degeneration, abscess or gland infarction.

MRI has the advantage of better elucidation of adjacent anatomical structures. It is the modality of choice for determining optic or cavernous sinus involvement. MRI is also helpful in evaluating the adjacent carotid arteries. If visual impairment is suspected, formal visual field testing should be undertaken. Urgent referral for MRI is required if visual deterioration occurs.

John was instructed not to drive until further notice. He underwent Humphrey visual field testing, which showed nonspecific defects in the periphery of the nasal superior quadrant in the right eye. These were not thought to be significant.

Is a lumbar puncture indicated?

Answer: Examination of the CSF is rarely helpful. It often reveals normal findings unless necrotic material or blood from the apoplectic tumour has reached the subarachnoid space. In this instance, patients can present with a clinical picture similar to a subarachnoid haemorrhage and present with meningism. CSF analysis would then show xanthochromia, red blood cells and high protein and/or low glucose levels. These features are not diagnostic.[1,3]

What therapy does John need for panhypopituitarism secondary to pituitary apoplexy in a non-functioning pituitary adenoma?

Answer: Acute secondary adrenal insufficiency is seen in approximately two-thirds of patients with pituitary apoplexy. It is the major source of mortality associated with this condition. Hypocortisolaemia blunts vascular responsiveness to adrenaline with resultant haemodynamic instability and risk of dangerous hypotension, particularly under superimposed physiological stress. As such, despite the seemingly mild presentation in a case such as John's, pituitary apoplexy constitutes an endocrine emergency. The patient should be referred to an emergency department for rapid haemodynamic stabilisation if indicated and for urgent endocrinology review.

Prompt corticosteroid replacement is critical. Patients with pituitary apoplexy are often unwell, with nausea and vomiting. Oral steroids may not be tolerated or well absorbed. Initially, intravenous hydrocortisone 50 mg or 50 mg intramuscularly 6 hourly may be required. This can be administered safely by a GP in his or her rooms, although such a patient should then be sent to a specialist facility for further care and assessment. Once the acute symptoms subside, hydrocortisone should be tapered to a standard maintenance dose of approximately 20 mg per day, usually in three divided doses. Dosing should be weighted towards the first part of the day (e.g. 12 mg at 7 am; 6 mg at 11 am; 4 mg at 2 pm) to best imitate physiological diurnal glucocorticoid secretion and to minimise sleep disturbance and long-term glucocorticoid excess complications. The patient's progress should be monitored. Given the aim of hydrocortisone therapy is to mimic the body's normal physiological production, it is unlikely that with ongoing observation John would be exposed to excessive doses of corticosteroid. Hence, replacement therapy should not cause significant increases in bone loss. Screening for osteoporosis and diabetes should be based on risk factor assessment.

Replacement therapy should be directed towards normalising the affected axes, typically thyroid and gonadal. Of note, to avoid precipitating an adrenal crisis, thyroid hormone replacement should only be instated after cortisol replacement has commenced.

Is there a role for surgery?

Answer: Patients with pituitary apoplexy who are without any neuro-ophthalmic signs or have only mild and stable signs can be considered for conservative management with careful monitoring. Patients with serious neuro-ophthalmic signs such as severely reduced visual acuity, severe and persistent or deteriorating visual field defects or deteriorating level of consciousness should be considered for urgent surgical decompression. Ocular paresis because of involvement of cranial nerves III, IV or VI in the cavernous sinus in the absence of visual field defects or reduced visual acuity is not in itself an indication for immediate surgery. Resolution will typically occur within days or weeks with conservative management.

John was referred for urgent neurosurgical review. As he did not have significant visual defects, surveillance with serial MRI brain scans was undertaken.

Three weeks after his diagnosis and initiation of therapy, John's appetite improved, he gained 3 kg in weight and his systolic pressure was 150 to 170 mmHg without a postural drop. Consequently, his antihypertensive therapy was recommenced. He continued to have poor libido and remained easily fatigued. He was approved to resume driving.

Once stabilised, John's hormone

Practice points

- Pituitary apoplexy is sudden haemorrhage or infarction of the pituitary, usually occuring in patients with a pre-existing nonfunctioning pituitary macroadenoma.
- As there is often clinical unawareness of the pre-existing adenoma, diagnosis may be difficult and delayed. Hypertension is the most common predisposing factor.
- Pituitary apoplexy is characterised by sudden onset of headache and vomiting. Patients with serious neuro-ophthalmic signs should be considered for urgent surgery.
- MRI is the radiological investigation of choice but CT is more commonly used in an acute clinical setting. Diagnostic difficulty may arise in distinguishing aneurysms from haemorrhage.
- Most patients with a pituitary adenoma have a deficiency of one or more of the anterior pituitary hormones. The most clinically important deficit is the low adrenocorticotrophic hormone level.
- Prompt corticosteroid replacement is critical. Initially, hydrocortisone intramuscularly 6 hourly may be required. This can be administered safely by a GP in their rooms, although such a patient should then be sent to a specialist facility for further care and assessment.
- Thyroid hormone replacement therapy and testosterone therapy are commonly required. Growth hormone deficiency is commonly seen, but replacement therapy is seldom given because of a lack of PBS funding.
- Patients require a medical alert bracelet and emergency identification card.
- Education of patients and their families is needed regarding not missing corticosteroid doses, increasing doses at times of stress, what to do when oral hydrocortisone can not be tolerated (e.g. if vomiting) and the importance of making the diagnosis known if undergoing surgery in future.

Table 2. Blood test results after cessation of thyroxine therapy

Test	Result	Reference range
Thyroid stimulating hormone (mIU/L)	0.88	0.5–4.0
Free thyroxine (T_4) (pmol/L)	14	10–20
Free triiodothyronine (T_3) (pmol/L)	4.6	3.5–6.0
Testosterone (nmol/L)	10	9.5–28
Insulin-like growth factor-1 (IGF-1) (nmol/L)	14	7–30
Prolactin (IU/mL)	201	40–450
Follicle stimulating hormone (mIU/mL)	6	<14
Luteinising hormone (mIU/mL)	1.9	<11

replacement therapy included: thyroxine 50 µg daily, hydrocortisone three times a day (12, 6 and 4 mg) and synthetic testosterone patch 5 mg/24 hours. Surveillance thyroid function testing and total testosterone levels indicated adequate hormonal replacement.

What further education should be provided for John?

Answer: Although the diagnosis of hypopituitarism secondary to pituitary apoplexy has now been made, it is important to avoid secondary adrenal crises in the future, which may occur in times of physical stress such as from infection or surgery. In these instances 'stress' doses of corticosteroids, usually double to triple the regular dose, may be required to mimic the physiological increase in cortisol typically secreted by the adrenal glands during times of illness.

During John's outpatient review, a medical alert bracelet and emergency identification card were organised. John underwent education on increasing his corticosteroid doses at times of illness. In the event that oral hydrocortisone could not be tolerated (e.g. if he was vomiting) he was instructed to present to a medical practitioner. In this instance rectal administration of prednisolone as an emergency option could be used. Alternatively, intramuscular hydrocortisone 100 mg may be administered.

John's wife also underwent education regarding his diagnosis. She was also taught how to administer the intramuscular hydrocortisone injection in the event of an emergency.

If John undergoes a general anaesthetic in future he must inform his anaesthetist and surgeon of the diagnosis. Intravenous hydrocortisone at induction of anaesthesia and ongoing parenteral doses while he is restricted to nil by mouth will be required.

The importance of not missing doses of corticosteroids was stressed as this can precipitate an adrenal crisis. Indications for stress dosing (e.g. double his regular dose) of hydrocortisone were emphasised.

Can John's pituitary function recover?

Answer: Studies have shown partial or complete recovery of pituitary function in up to 50% of patients, irrespective of surgical or medical management, although some data exist that favour greater pituitary recovery after surgery. This has been attributed to the release of pressure on the portal vessels post surgery. Data suggest that the type of long-term hormone replacement therapy needed after pituitary apoplexy is glucocorticosteroids in 60 to 80% of patients, thyroid hormone in 50 to 60% and testosterone in 60 to 80% of men.[4] Growth hormone (GH) deficiency is commonly seen, but replacement therapy is seldom given because of a lack of PBS funding. A recent study examined the effect of GH replacement under a publicly funded scheme over a three-year period. The researchers reported improved quality of life and decreased waist circumference in all patients, showing that potential benefits may be achieved with replacement therapy.[5] Patients treated for apoplexy should have an annual biochemical assessment of pituitary function including measurement of levels of free T_4, TSH, LH, follicle stimulating hormone, testosterone in men, oestradiol in women, prolactin, IGF-1 and dynamic tests of cortisol and growth hormone secretion if clinically appropriate. An important practice point is that thyroxine doses should be adjusted based on T_4 levels, as TSH levels in secondary hypothyroidism will be consistently low. Visual defects can also improve over time, depending on severity, and should be periodically reassessed.[1,6]

Outcome: In summary, this is a case of subacute pituitary apoplexy presenting relatively insidiously with nonspecific symptoms. Further investigation revealed radiological evidence of pituitary apoplexy, with pituitary dysfunction across multiple axes, requiring hormone replacement therapy. The seriousness of this condition required specialist referral, with ongoing patient and family education as to the importance of continual therapy and monitoring and emergency sick day management strategies.

By his two-year follow up, John had been successfully weaned off his thyroxine replacement. His dose of hydrocortisone was dropped to 10, 6, and 2 mg three times a day. He continued on testosterone replacement. John's blood test results after cessation of thyroxine therapy are shown in Table 2. **ET**

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COMPETING INTERESTS: None.