CASE REPORTS

The clinical features and management of pituitary apoplexy

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Summary

The clinical features and management of three patients presenting with pituitary apoplexy are described. They illustrate the difficulty of differentiating pituitary apoplexy from other acute neurological conditions. One of the patients is the first reported case of pituitary apoplexy occurring in a histologically proved craniopharyngioma. Two of the cases reported were treated conservatively and recovered without serious sequelae. It is suggested that it is not always necessary to consider pituitary apoplexy as a neurosurgical emergency. The relationship between radiotherapy and pituitary apoplexy is discussed.

Introduction

Acute massive infarction of a pituitary tumour is a rare condition in which the clinical picture of headache, drowsiness and visual disturbances may be confused with other acute neurological conditions, principally pyogenic meningitis and subarachnoid haemorrhage. If the correct diagnosis is not made and appropriate treatment instituted, the patient may die or suffer permanent visual impairment. It has become evident, however, that pituitary apoplexy has a wide clinical spectrum, not only in its mode of presentation but also in its outcome. Previous reports have stressed the high mortality of the condition and the need to regard it as a neurosurgical emergency. While this is true for some patients, others have recovered spontaneously or after delayed surgical intervention without apparent ill effect.

Three patients are here described who had pituitary apoplexy. Each posed an initial diagnostic problem, two recovered spontaneously but the third required craniotomy. The clinical details are set out below.

Case 1

A 65-year-old, previously fit man developed abdominal pain, and difficulty in micturition,

followed 24 hr afterwards by meningeal symptoms, diplopia, hiccoughs and vomiting. On admission to hospital 2 days later, he was febrile, drowsy and unco-operative. There was marked neck stiffness, and right third and left sixth nerve palsies. Initial investigations are shown in Table 1.

On transfer to The London Hospital 7 days later, following demonstration of enlargement of the pituitary fossa, he was drowsy. There were no signs of long-standing hypopituitarism and his blood pressure was 100/60 mmHg without postural fall. His ocular palsies were still present. His fundi were normal and static perimetry revealed a left temporal hemianopia. His visual acuity was 6/9 in the right and 6/12 in the left eye.

Pituitary apoplexy was provisionally diagnosed. Bilateral carotid angiograms, orbital venogram and air encephalogram under steroid cover delineated a pituitary tumour which extended into the right cavernous sinus and above the sella turcica posteriorly. Subarachnoid haemorrhage from a vascular malformation or aneurysm was excluded. As considerable improvement in his confusion and left sixth palsy had occurred in 2 days and as his visual acuity was stable, he was treated conservatively. Subsequently the diagnosis of hypopituitarism was confirmed by the absence of rises in growth hormone (peak level 5 µg/l) and cortisol (peak level 0.03 nmol/l = 1 µg/100 ml) despite adequate insulin-induced hypoglycaemia (minimum blood sugar 1.4 mmol/l = 25 mg/100 ml). Thyroid function tests revealed hypothyroidism. Replacement therapy with cortisol and thyroxine was begun and, in an attempt to prevent further tumour growth, he was given 4,500 rad to the pituitary fossa. When last seen he was well, his ocular palsies had resolved, his visual fields were full and his visual acuity was unchanged. He continues on the replacement therapy.

Case 2

A 36-year-old garage director developed sudden, severe headache and diplopia. The symptoms became worse the next day, when fever and vomiting began.

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TABLE 1. Initial investigations

	Case 1	Case 2	Case 3
Cerebrospinal fluid			
Appearance	Xanthochromic	Not examined	Turbid
Protein	1.8 g/l		1.42 g/l
Glucose	10 mmol/l		—
Red cells	58 mm ⁻³		80 mm ⁻³
Polymorphs	4 mm ⁻³		320 mm ⁻³
Lymphocytes	1 mm ⁻³		80 mm ⁻³
Plasma sodium	126 mmol/l	130 mmol/l	Initially normal 4 days later 126 mmol/l
Skull X-ray	Enlargement of pituitary fossa	Enlargement of pituitary fossa, mandible and frontal sinuses	Gross enlargement of pituitary fossa, suprasellar specks of calcium

Conversion : SI to traditional units. Glucose: 1 mmol/l = 18 mg/100 ml.

Five days later he developed profuse diarrhoea and hiccoughs. He was admitted to hospital the following day. He appeared ill and was febrile (40°C). Acromegalic facies were noted. Glandular fever was diagnosed on the basis of a lymphocytosis and a positive Paul Bunnell test. He recovered without treatment and was discharged after 11 days. A week later he was re-admitted with a history of 2 days of confusion, choreiform movements and hiccoughs. These were considered to be due to glandular fever encephalitis. Lumbar puncture was not performed and, having recovered spontaneously, he was discharged after 10 days.

He was admitted to The London Hospital 6 weeks after the start of his illness for investigation of acromegaly. Prognathism had been noted 9 years before, his shoe size had increased over the following 5 years, and he had developed bilateral carpal tunnel syndrome. He had two children aged 10 and 2½ years and denied loss of libido, previous headaches or visual disturbance. There were characteristic bone changes but his skin was fine and non-greasy. He was euthyroid, normotensive, and there were no abnormal neurological signs. During an insulin tolerance test his blood sugar fell to 1 mmol/l (17 mg/100 ml) but plasma cortisol rose to only 0.22 µmol/l (8 µg/100 ml) and serum growth hormone to 7 µg/l. Growth hormone remained low throughout a glucose tolerance test. Thyroid function tests were normal but there was an impaired TSH response to TRH (peak level 2.5 mu./l at 20 min). Skull X-ray showed considerable enlargement of the sella turcica which had a double floor. As his visual acuity was unimpaired and his visual fields were full on perimetry, he was treated conservatively with replacement cortisol and fluoxymesterone, and has returned to work and is clinically well. The acute episode has been previously reported (Belchetz and Stuart Mason, 1972).

Case 3

A 29-year-old woman was admitted to hospital having been well until 4 days previously when she suddenly developed a severe headache and vomiting. She was ill, febrile, drowsy and had neck rigidity. She was clinically hypothyroid and lacked body hair. Her right optic disc was pale and she had a right temporal field defect on confrontation. Treatment with antibiotics for presumed pyogenic meningitis produced no improvement until hydrocortisone was added.

She was transferred to The London Hospital when a skull X-ray revealed an expanded pituitary fossa. On admission she was drowsy but easily roused. She was of normal height (1.60 m) but clinically showed features of hypopituitarism. Both optic discs were pale and perimetry revealed bitemporal hemianopia. Her visual acuity was 6/18 in the right eye and 6/9 in the left eye. She denied any symptoms other than amenorrhoea before this episode. Her periods had begun when she was 15 years old and stopped 1 year later, at which time her body hair regressed, and she had experienced frequent headaches for a few months.

The pituitary fossa was grossly enlarged on X-ray and small calcified flecks were seen above the posterior clinoid processes. Her vision failed to improve and 24 days after the onset of illness, craniotomy under steroid cover was performed. A large, suprasellar, necrotic tumour, distorting the right optic nerve was found and aspirated. A small amount of solid tumour was found within the fossa which subsequent histology showed to be part of a craniopharyngioma. Postoperative recovery was uneventful and her visual acuity improved. The pituitary fossa was irradiated (4500 rad) because of incomplete tumour removal, and she was discharged on thyroxine and corticosteroid replacement.

One month later she was re-admitted with a 5-day

TABLE 2. Clinico-pathological features in pituitary apoplexy

Pathological change	Clinical sequelae
Leakage of blood into subarachnoid space	Features of subarachnoid haemorrhage } (Adriano and Al-Mondhiry, 1967; Epstein <i>et al.</i> , 1971; Uihlein, Balfour and Donovan, 1957; List, Williams and Balyeat, 1952)
Leakage of necrotic tissue into subarachnoid space	
Destruction of pituitary tissue	Hypopituitarism (Adriano and Al-Mondhiry, 1967)
Pressure on: (a) Optic chiasm and tracts	Visual field defects, impaired visual acuity (Robinson, 1972)
(b) Cranial nerves 3, 4 and 6	Ocular palsies (Symonds, 1962)
(c) Internal carotid and its branches	Hemiplegia (Schnitker and Lehnert, 1952; Jefferson and Rosenthal, 1959)
(d) Hypothalamus	Hyperpyrexia, mental confusion, impaired water balance (Jefferson, 1940)

history of increasingly severe headache, vomiting and deteriorating vision. On admission she was drowsy, unable to perceive light in her right eye and had a temporal hemianopia on the left. Large doses of dexamethasone resulted in some visual improvement. At re-exploration of her pituitary fossa gelatinous material was aspirated. Postoperatively her visual acuity rapidly improved, but she developed diabetes insipidus which was easily controlled by vasopressin. Thirty months after the first episode her visual acuity was 6/18 on the right and 6/12 on the left, with a persistent right temporal field defect. She was well, taking thyroxine, cortisol and vasopressin.

Discussion

The diagnostic problems and spontaneous recovery of some patients with pituitary apoplexy lead to a probable underestimate of its frequency. After the first description in 1905 (Bleibtreu, 1905), early reports were predominantly of eosinophilic tumours (Brougham, Heusner and Adams, 1950), but of ninety-three cases reported recently in which the histology of the tumour is known, only twenty-three were eosinophilic while sixty-eight were chromophobic and two were basophilic adenomas (Wright, Ojemann and Drew, 1965; Adriano and Al-Mondhiry, 1967; Epstein *et al.*, 1971; Rovit and Fein, 1972; Robinson, 1972; Dawson and Kothandaram, 1972; Sakalas *et al.*, 1973). Case no. 3 is the first proved craniopharyngioma undergoing pituitary apoplexy. Whether this distribution of cell types indicates propensity to apoplexy rather than the relative prevalence of the different tumours is unclear.

Pathogenetic factors in pituitary apoplexy may include tumour necrosis due to outgrowth of blood supply (Brougham *et al.*, 1950), or impaction at the diaphragmatic notch jeopardizing portal vessels (Rovit and Fein, 1972). Apoplexy has also been associated with head injury (Van Wagenan, 1932), anticoagulants (Nourizadeh and Pitts, 1965), irradiation (Uihlein, Balfour and Donovan, 1957; Shenkin, 1955), pregnancy (Kajtar and Tomkin,

1971) and upper respiratory tract infections (Dawson and Kothandaram, 1972).

The varied clinical features associated with pituitary apoplexy are summarized in Table 2. The most common are sudden severe headache, altered state of consciousness and ocular symptoms. Confusion with meningitis, subarachnoid haemorrhage and encephalitis is illustrated by the three patients. The diagnostic importance of the expanded sella turcica underlines the value of a skull X-ray in such acute neurological episodes. Features suggestive of subarachnoid haemorrhage may nevertheless necessitate carotid angiograms to exclude the co-existence of a pituitary tumour with a bleeding aneurysm. A carotid artery aneurysm may expand the sella turcica indistinguishably from a pituitary tumour (White and Ballantine, 1961). Untreated adrenal insufficiency no doubt contributed to the high mortality of cases reported before the advent of corticosteroid therapy. It is essential to begin treatment with hydrocortisone as soon as the diagnosis is entertained and to ensure adequate steroid cover during stressful investigations or surgery. Some patients, for example cases 1 and 2, may not develop adrenal failure during the acute episode but can subsequently be shown to have impaired pituitary function.

It has been stated that pituitary apoplexy should always be treated as a neurosurgical emergency (Epstein *et al.*, 1971; Shenkin, 1955). However, some patients treated conservatively have recovered without serious sequelae (Wright *et al.*, 1965; Fountain, Baird and Poppen, 1951), with a subsequent re-ossification of the sella turcica in three (Dawson and Kothandaram, 1972; List, Williams and Balyeat, 1952; Krueger, Ungar and Roswit, 1960). One patient with the Forbes-Albright syndrome experienced regression of her symptoms and improvement in pituitary function following an apoplectic episode which was treated conservatively (McLaren and Keet, 1973). Patient 2 remained euthyroid on follow-up, and it would therefore seem that panhypopituitarism is not an inevitable sequel to pituitary apoplexy.

A patient who presents with pituitary apoplexy requires corticosteroids and careful observation. Deterioration in level of consciousness, visual acuity or visual fields are indications for surgery, while other focal signs, e.g. ophthalmoplegia, often recover spontaneously (Symonds, 1962). Furthermore, surgical intervention need not be an emergency procedure to ensure restoration of vision (Robinson, 1972). Observation of the patient allows medical preparation and such further radiological investigations that may be indicated.

Irradiation of pituitary tumour has been implicated as a cause of pituitary apoplexy (Shenkin, 1955). Thirteen of seventy cases in one series had received previous irradiation (Uihlein *et al.*, 1957). Poppen (1963), however, on reviewing 360 patients with pituitary tumours found thirty-eight cases of pituitary apoplexy, but in only two of these could it be related to radiotherapy. Poor response to irradiation by tumour having undergone necrosis has been suggested (Poppen, 1963; Pennybacker, 1961). Others consider that irradiation is absolutely contra-indicated because of the suggested causal relation between it and pituitary apoplexy (Schurr, 1966). However, there have been reports of patients irradiated after the apoplectic episode without ill effect and with subsequent improvement. Patient no. 1 can be included in this category. Radiotherapy was given to patient no. 3 because of incomplete tumour removal, irradiation having been claimed to delay recurrence of craniopharyngioma (Hoff and Patterson, 1972). It is impossible to say if the refilling of the cystic tumour was related to the course of irradiation completed 28 days before her sudden deterioration of vision. Although the relationship of irradiation to pituitary apoplexy remains unproved, it clearly must be borne in mind when radiotherapy is given to the pituitary.

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References

ADRIANO, H.C. & AL-MONDHIRY, H.A.B. (1967) Hemorrhagic necrosis in pituitary tumors (pituitary apoplexy). *New York Journal of Medicine*, **61**, 1448.

BELCHETZ, P.E. & STUART MASON, A. (1972) Acromegaly and pituitary apoplexy. *Proceedings of the Royal Society of Medicine*, **65**, 984.

BLEIBTREU, L. (1905) Ein Fall von Akromegalie (Zerstörung der Hypophysis durch Blutung). *Münchener medizinische Wochenschrift*, **52**, 2079.

BROUGHAM, M., HEUSNER, A.P. & ADAMS, R.D. (1950) Acute degenerative changes in adenomas of the pituitary body—with special reference to pituitary apoplexy. *Journal of Neurosurgery*, **7**, 421.

DAWSON, B.H. & KOTHANDARAM, P. (1972) Acute massive infarction of pituitary adenomas. *Journal of Neurosurgery*, **37**, 275.

EPSTEIN, S., PIMSTONE, B.L., DE VILLIERS, J.C. & JACKSON, W.P.U. (1971) Pituitary apoplexy in five patients with pituitary tumours. *British Medical Journal*, **2**, 267.

FOUNTAIN, E.M., BAIRD, W.C. & POPPEN, J.L. (1951) Pituitary apoplexy: a report of three cases with recovery. *Lahey Clinic Bulletin*, **7**, 117.

HOFF, J.T. & PATTERSON, R.H. (1972) Craniopharyngiomas in children and adults. *Journal of Neurosurgery*, **36**, 299.

JEFFERSON, G. (1940) Extrasellar extensions of pituitary adenomas. *Proceedings of the Royal Society of Medicine*, **33**, 433.

JEFFERSON, M. & ROSENTHAL, F.D. (1959) Spontaneous necrosis in pituitary tumours (pituitary apoplexy). *Lancet*, **i**, 342.

KAJTAR, T. & TOMKIN, G.H. (1971) Emergency hypophysectomy in pregnancy after induction of ovulation. *British Medical Journal*, **4**, 80.

KRUEGER, E.G., UNGAR, S.M. & ROSWIT, B. (1960) Hemorrhage into pituitary adenoma with spontaneous recovery and reossification of the sella turcica. *Neurology*, **10**, 691.

LIST, C.F., WILLIAMS, J.R. & BALYEAT, G.W. (1952) Vascular lesions in pituitary adenomas. *Journal of Neurosurgery*, **9**, 177.

MCLAREN, E.H. & KEET, P.C. (1973) Regression of the Forbes-Albright syndrome after pituitary apoplexy. *British Medical Journal*, **2**, 314.

NOURIZADEH, A.R. & PITTS, F.W. (1965) Hemorrhage into pituitary adenoma during anticoagulant therapy. *Journal of the American Medical Association*, **193**, 623.

PENNYBACKER, J. (1961) The treatment of pituitary tumours. *Proceedings of the Royal Society of Medicine*, **54**, 619.

POPPE, J.L. (1963) Changing concepts in the treatment of pituitary adenomas. *New York Academy of Medicine*, **39**, 21.

ROBINSON, J.L. (1972) Sudden blindness with pituitary tumors. Report of three cases. *Journal of Neurosurgery*, **36**, 83.

ROVIT, R.A. & FEIN, J.M. (1972) Pituitary apoplexy: a review and reappraisal. *Journal of Neurosurgery*, **37**, 280.

SAKALAS, R., DAVID, R.B., VINES, F.S. & BECKER, D.P. (1973) Pituitary apoplexy in a child. *Journal of Neurosurgery*, **39**, 519.

SCHNITKER, M.T. & LEHNERT, H.B. (1952) Apoplexy in a pituitary chromophobe adenoma producing the syndrome of middle cerebral artery thrombosis. *Journal of Neurosurgery*, **9**, 210.

SCHURR, P.H. (1966) Pituitary tumours in man. In: *The Pituitary Gland Vol. 2* (Ed. by G. W. Harris and B. T. Donovan), p. 498. Butterworths, London.

SHENKIN, H.A. (1955) Relief of amblyopia in pituitary apoplexy by prompt surgical intervention. *Journal of the American Medical Association*, **159**, 1622.

SYMONDS, C. (1962) Ocular palsy as the presenting symptom of pituitary adenoma. *Bulletin of the Johns Hopkins Hospital*, **111**, 72.

UIHLEIN, A., BALFOUR, W.M. & DONOVAN, P.T. (1957) Acute hemorrhage into pituitary adenomas. *Journal of Neurosurgery*, **14**, 140.

VAN WAGENAN, W.P. (1932) Hemorrhage into a pituitary tumor following trauma. *Annals of Surgery*, **95**, 625.

WHITE, J.C. & BALLANTINE, H.T. (1961) Intraseellar aneurysms simulating hypophyseal tumors. *Journal of Neurosurgery*, **18**, 34.

WRIGHT, R.L., OJEMANN, R.J. & DREW, J.H. (1965) Hemorrhage into pituitary adenomata. *Archives of Neurology*, **12**, 326.