Clinical Problems

Pituitary Apoplexy in Five Patients with Pituitary Tumours

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Summary

Five cases of pituitary apoplexy occurring in patients with pituitary tumours are described. This uncommon condition is characterized by headache, sudden loss of vision, alteration in the level of consciousness, and usually an abnormal cerebrospinal fluid. The whole picture may be complicated by endocrine dysfunction. The diagnosis is strengthened by a radiologically abnormal pituitary fossa and confirmed by the operative finding of haemorrhagic necrotic tissue. Surgical decompression under steroid cover offers the only hope of restoration of vision. Frequent postoperative follow-up is obligatory.

Introduction

Chronic degenerative changes in pituitary adenomas take the form of colloid cystic degeneration, reparative fibrosis probably secondary to ischaemic necrosis, and calcification. They are held responsible for the arrest or "burning out" of activity in a pituitary tumour such as occurs occasionally in acromegaly, as well as the rare development of partial or complete hypopituitarism (Kraus, 1945; Brougham *et al.*, 1950).

Occasionally infarction in a pituitary tumour or haemorrhage with or without infarction has led to the clinical syndrome of pituitary apoplexy. The symptomatology is usually typical, with a sudden onset of or worsening of headache, sudden deterioration of vision, ocular palsies, confusion, drowsiness, or coma, and thus may be confused with subarachnoid haemorrhage or meningitis. There may or may not have been previous evidence of pituitary dysfunction. With the development of coma hyperpyrexia may ensue and death is not unusual, particularly if cortisol insufficiency is not treated.

Previous evidence of pituitary dysfunction, an expanded pituitary fossa on skull x-ray examination, and an abnormal cerebrospinal fluid strengthen the diagnosis. A patient being treated for a pituitary adenoma by radiotherapy is particularly prone to this complication. With a knowledge of the clinical picture and liaison between physician and neurosurgeon death, permanent blindness, or other neurological defect may be prevented. Prompt surgical decompression not only relieves the acute pressure on vital intracranial structures but also confirms the diagnosis of pituitary apoplexy by finding a haemorrhagic necrotic tumour. Five patients have recently been seen with this syndrome at Groote Schuur Hospital. Their case details appear below.

Case 1

A man aged 65 complained of a sudden severe frontal headache four days before admission. Two days later he became totally blind in both eyes, vomited, and felt feverish. On examination he was seen to be drowsy and confused, with a temperature of 102°F (38.9°C) and a blood pressure of 95/65 mm Hg. Severe neck stiffness and a positive Kernig's sign were present. The optic discs were normal and showed no papilloedema or atrophy. Both pupils were fixed and dilated. Eye movements were normal. Haemoglobin was 16 g/100 ml, white blood count 19,500/mm³ (70% polymorphs), and E.S.R. 112 mm/hour (Westergren). Cerebrospinal fluid was clear, with protein 65 mg/100 ml, globulin ++, chloride 619 mEq/l., normal sugar, and a cell content of 210 polymorphs and 210 lymphocytes/mm³. X-ray examination of the skull showed a large pituitary fossa with an irregular floor. Carotid angiography showed the proximal anterior cerebral vessels to be displaced upwards by a suprasellar extension of an intrasellar mass. Craniotomy was immediately performed under cover of intravenous hydrocortisone, a large necrotic pituitary adenoma being found. The tumour capsule was incised and the contents were sucked out to decompress the optic nerves. Histological examination showed completely necrotic fragments with no recognizable neoplasm or pituitary tissue.

Postoperatively the vision improved in the right eye over five days but the patient remained completely blind in the left. He was discharged on hydrocortisone 10 mg twice daily. One year later he was readmitted for reassessment and found to be mildly diabetic. Two weeks after hydrocortisone had been stopped the following pituitary function tests were carried out. Urinary follicle-stimulating hormone less than 6 mouse units (normal 6-48). Metapyrone test: basal urinary oxogenic steroids 4.3 mg/24 hours; post-metapyrone urinary oxogenic steroids 5.1 mg/24 hours. Insulin test was terminated because of severe hypoglycaemia. Growth hormone was not detected during the test. Lysine-vasopressin (10 units intramuscularly) test: plasma cortisol at 0, 30, and 60 minutes were 13, 8, and 12 µg/100 ml respectively. ¹³¹I thyroid uptake 19% and 42% at 6 and 24 hours. The patient thus had a deficiency of pituitary-adrenal reserve as well as of gonadotrophin and growth hormone. Thyroid function was normal. He was accordingly discharged on hydrocortisone 10 mg twice daily and a diabetic diet and has remained well with 6/18 vision in the right eye but none in the left.

Case 2

A Bantu man aged 25 was referred to Groote Schuur Hospital from a peripheral hospital with the history that one month before admission he experienced a sudden onset of occipital and vertical headache. Two weeks later he became suddenly and totally blind. Thereafter (the time interval is not clear) he underwent craniotomy and pituitary decompression. Histological findings were reported as "fragments of pituitary gland with no evidence of neoplasm."

The patient was then referred to Groote Schuur Hospital for consideration of radiotherapy and for assessment of pituitary function. He was found to be thin, drowsy, and completely blind, with slurred speech. Temperature was normal. Blood pressure was 100/70 mm Hg. Cranial nerves were intact except for widely dilated, poorly reacting pupils. Both fundi showed optic atrophy. Haemoglobin was 16 G/100 ml, white blood count 8,900/mm³, and E.S.R. 30 mm/hour (Westergren). Cerebrospinal fluid was normal. Pituitary function tests: urinary 17-oxosteroids 2.1 mg/24

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hours, urinary 17-oxogenic steroids 0.3 mg/24 hours. Insulin tolerance test: plasma cortisol 5, 3, 6, and 4 μ g/100 ml, and blood sugar 62, 42, 34, and 30 mg/100 ml before and 20, 40, and 60 minutes after insulin. Plasma cortisol: 8 a.m. 1 μ g/100 ml, midnight 2 μ g/100 ml. Thyroid function tests: protein-bound iodine 2 μ g/100 ml, 24-hour 131 I uptake 12%. Serum electrolytes: sodium 124 mEq/l., potassium 4.7 mEq/l. Cholesterol 226 mg/100 ml, serum osmolality 237 milliosmoles/l. X-ray examination of the skull showed a greatly enlarged pituitary fossa with erosion of the posterior clinoids. The anterior clinoids and floor of the fossa appeared intact.

The patient was submitted to radiotherapy but six weeks later was readmitted; he was hypotensive, grossly withdrawn, and slightly confused. He improved on antidepressants and intravenous and oral hydrocortisone. He was discharged on permanent hydrocortisone 20 mg twice daily and thyroxine 0.2 mg daily.

Case 3

Three weeks before admission a 48-year-old woman developed sudden pain over the left temple lasting a few hours. On awakening the following morning she found that she could barely see. Vision remained poor but headache did not recur. On examination she was seen to be fully conscious with normal temperature. Blood pressure was 118/70 mm Hg. She could discern only gross hand movements in the nasal half of the fields and had complete bitemporal blindness. Early optic atrophy was found. Haemoglobin was 13.5 g/100 ml. E.S.R. was 60 mm/hour (Westergren). White cell count was normal. Cerebrospinal fluid was clear, colourless, and without clot or white cells; the protein was 20 mg/100 ml, globulin negative, chloride 119 mEq/l., and glucose 113 mg/100 ml. Wassermann reaction was negative. X-ray examination of the skull showed an enlarged pituitary fossa with erosion of its floor and of the posterior clinoids. A right carotid angiogram showed displacement of the anterior cerebral artery, indicating a large pituitary mass with considerable suprasellar extension.

At operation a large pituitary tumour with suprasellar extension was removed, which on histological examination consisted of numerous fragments of haemorrhagic tissue, resembling a chromophobe adenoma. The patient's vision did not improve and, in fact, she remained almost completely blind. Fifteen days postoperatively she developed a deep-vein thrombosis of the leg and died suddenly one day later. Necropsy showed a pulmonary embolus. No undue haemorrhage was found at the site of the operation.

Case 4

Six weeks before admission a 25-year-old woman noticed that her sight was becoming poorer and that at times she was totally blind. Three weeks later she suffered a severe headache lasting three days. One week before admission she became completely blind in her right eye and remained so, while the vision in her left eye diminished, especially on lateral gaze. On examination she was seen to be fully conscious with normal temperature. Blood pressure was 145/100 mm Hg. Optic atrophy was seen in both discs. Haemoglobin was 13.5 g/100 ml, E.S.R. 20 mm/hour (Westergren), and white blood count 5,450/mm³. Cerebrospinal fluid was clear, with a protein of 20 mg/100 ml, globulin negative, normal sugar, and 1 lymphocyte and 1 monocyte/mm³. Wassermann reaction was negative. Examination of visual fields showed a bitemporal hemianopia. X-ray examination of the skull showed a large pituitary fossa. Serum electrolytes were normal.

At operation a pituitary tumour was incised; dark blood escaped from it and it was then removed by suction. Histological examination: specimens consisted of scanty fragments of brown tissue up to 4 mm in diameter; groups of cells were seen which were suggestive of a chromophobe adenoma. Postoperatively the patient's visual fields greatly improved, and she was discharged well. No further follow-up material is available.

Case 5

A man aged 69 was in perfect health three days before admission until he woke up with pain in the left supraorbital region. The left eye was puffy, and one day later vision in that eye had noticeably deteriorated. The disc margins were sharply defined and there

was slight temporal pallor. X-ray films taken to exclude sinusitis showed pronounced enlargement and erosion of the sella. At this time he complained of diplopia and was noted to have a left inferior oblique nerve palsy.

On the third day after the onset of symptoms he was admitted to hospital with complete ptosis of the left eye, and had evidence of meningeal irritation, stupor, and Cheyne-Stokes respiration. He showed the general features of hypopituitarism—a pale soft finely wrinkled skin, scanty pubic, axillary, and facial hair, and atrophied external genitalia. A lumbar puncture produced slightly blood-stained cerebrospinal fluid at a pressure of 220 mm Hg. At midday on the day of admission he was completely unresponsive to all forms of stimulation, with a total ophthalmoplegia on the left and some right-sided weakness. He had several right-sided seizures. Hydrocortisone was begun and maintained until he died. During the next three days his respiration deteriorated so much that a tracheostomy was performed. He remained on the respirator for five days, after which he gradually improved during the next month. One month after admission there was no right third nerve weakness. The pupillary dilatation was due to amblyopia on that side. Both discs were pale but not dead white. There was a mild right hemiparesis affecting the face, arm, and leg.

It was suspected that the patient had a pituitary tumour which had undergone infarction and had expanded into the left cavernous sinus causing some disturbance of function of the left internal carotid artery. Angiography showed elevation of the anterior cerebral artery, characteristic of a pituitary tumour. A craniotomy was performed and a rather pale tumour was found lying snugly against the optic nerves. Necrotic tissue was taken from the tumour for histological examination. Both optic nerves were completely freed. Postoperatively the patient initially improved though he soon relapsed into stupor. Return of vision was doubtful. Seven months after his original ictus he suddenly died. Necropsy was not performed.

Discussion

PATHOLOGY

The causal mechanism whereby pituitary adenomas undergo haemorrhagic necrosis is not known, but it is presumed to be due to the growth rate of the neoplastic cells outstripping the vascular supply and producing ischaemic necrosis. Once infarction has occurred the tumour becomes a necrotic and/or haemorrhagic mass which expands beyond the size of the original adenoma. This sudden expansion and rise in intracapsular tension produces acute compression of neighbouring optic nerves, chiasma, and optic tract, which may already have been compromised by the pre-existing adenoma. Pressure may be exerted laterally on the cavernous sinus. If the haemorrhagic tumour or clot formation extends into the suprasellar subarachnoid space the third nerve and carotid artery may be involved. At this site sudden suprasellar extension of the tumour may compress the hypothalamus and add the effects of somnolence, confusion, and hypothermia to the clinical picture. Blood escaping into the basilar subarachnoid space may set up an inflammatory reaction in the subarachnoid cisterns.

The tumours of the pituitary which undergo apoplexy are usually chromophobe and eosinophilic adenomas, with perhaps a preponderance of the latter (Brougham *et al.*, 1950). No such changes have been reported in basophilic, fetal cell, or transitional cell adenomas (Brougham *et al.*, 1950). The histological picture is complicated by the fact that after haemorrhage and infarction have occurred it is difficult to identify the character and origin of the tumour tissue. The histological diagnosis of malignancy, which is extremely difficult in intact pituitary tumours, is made well-nigh impossible in haemorrhagic necrotic tissue.

CLINICAL SPECTRUM

Severe headache is almost invariable (see Table). This may be due to an acute swelling of the pituitary neoplasm or to meningeal irritation produced by subarachnoid haemorrhage. The

Summary of Important Clinical Features in 5 Cases of Pituitary Apoplexy

Case No.	Headache	Level of Consciousness	Optic Atrophy	Clinical Hypopituitarism	Abnormal Cerebrospinal Fluid	Abnormal Pituitary Fossa
1	+	Confused	+	—	+	+
2	+	Drowsy	+	—	—	+
3	+	Fully conscious	+	—	—	+
4	+	Fully conscious	+	—	—	+
5	+	Stuporous	+	+	+	+

+ = Present. — = Absent.

Note: Lumbar puncture was performed in Cases 2, 3, and 4 on presentation to Groote Schuur Hospital, weeks after the initial episode.

localization and character of the headache varies from patient to patient. All our patients gave such a history which varied in site and included frontal, temporal, and occipital localization.

Altered States of Consciousness.—This has been reported in other series to be the most frequent neurological abnormality (Brougham *et al.*, 1950). Three of our patients had altered levels of consciousness, taking the form of drowsiness, confusion, and frank coma. Death may occur. The progression from confusion to coma may take hours. Why altered levels of consciousness occur is not entirely clear but may be related to subarachnoid haemorrhage, compression of hypothalamic structures, raised intracranial pressure from obstructive hydrocephalus, or an acute attack of adrenal insufficiency accompanied by hypotension and hypoglycaemia (Brougham *et al.*, 1950).

Ocular Symptoms.—Visual acuity may be partially or totally impaired in either one or both eyes. Ophthalmoplegia may also be unilateral or bilateral. The oculomotor nerve is involved more often than the abducens (Brougham *et al.*, 1950; Symonds, 1962). Optic atrophy is common and was seen in four of our patients. Pre-existing defective vision may be present for years before the onset of ischaemic necrosis of the pituitary and the further rapid deterioration of vision.

Other Neurological Manifestations.—Neck stiffness and a positive Kernig's sign may occur, as in two of our patients. The clinical picture may mimic an aneurysmal subarachnoid haemorrhage (Kirschbaum and Chapman, 1948). Hemiplegia and aphasia (Brougham *et al.*, 1950; List *et al.*, 1952) have also been documented, and our Case 5 had a right-sided hemiparesis. This is usually attributed to involvement of the internal carotid artery, but the exact pathological process is far from clear. It may be the result of arterial spasm.

Endocrine Dysfunction.—Pituitary apoplexy has been described as occurring in patients with acromegaly (Bleibtreu, 1905; Kirschbaum and Chapman, 1948) and hypopituitarism (List *et al.*, 1952). Only one of our patients (Case 5) presented initially with the stigmata of pre-existing hypopituitarism. The subsequent course, however, may be complicated by symptoms and signs of hypoglycaemia, hypotension, and hypothermia, all of which may be attributable to the lack of secretion of pituitary trophic hormones. Three of our patients required permanent hormonal replacement for their consequent endocrine deficiencies.

Cerebrospinal Fluid.—The cerebrospinal fluid is usually abnormal (Brougham *et al.*, 1950; List *et al.*, 1952). It may be colourless, frankly blood-stained, or xanthochromic. An excess of white and red blood cells may be seen. Both the protein content and the pressure may be raised. Two of our patients showed an abnormal cerebrospinal fluid, but the remaining three were seen only weeks after the initial episode.

Radiological Picture.—All our patients had enlarged eroded pituitary fossae on x-ray examination.

Other Findings.—Nausea and vomiting occurred in one of our patients. This may have been related to meningeal irritation, increased intracranial pressure, a hypothalamic disturbance, or hypoadrenalism. Hyperpyrexia may be related to subarachnoid haemorrhage or to a disturbance of temperature regulation by an irritated or injured hypothalamus (List *et al.*, 1952). A raised temperature was seen in Case 1. A polymorph leucocytosis is commonly reported. Our only patient with a

raised white cell count was seen shortly after the onset of symptoms.

TREATMENT

The management of any neurological sequelae arising from pituitary apoplexy is essentially surgical and should be regarded as a neurosurgical emergency. Vision which has been lost in the acute episode of pituitary apoplexy may be regained by prompt decompression of the enlarged necrotic haemorrhagic tumour (Shenkin, 1955; Uihlein *et al.*, 1957). The main objective of surgical attack in pituitary tumour has always been the relief of pressure on the visual pathways, and the same principle holds when pituitary apoplexy occurs. In the past surgical treatment has been delayed because of the patient's poor general state which rendered diagnostic procedures and major surgery too risky. In the older literature on this subject existing hypopituitarism was regarded as a contraindication to surgery (List *et al.*, 1952). With the advent of hormonal substitution therapy it has become possible to be far more aggressive in this condition. The best policy is probably to bear only two considerations in mind—firstly, the degree of visual loss and, secondly, the degree of pituitary hypofunction. If there is rapid and severe loss of sight surgery has only to be postponed until the patient has been adequately resuscitated and covered by adrenocorticosteroids. There are cases on record (Krueger *et al.*, 1960) which for one reason or another were treated expectantly. They did not die, probably because they had an adequate remnant of pituitary tissue to maintain a normal physiological state.

It is mandatory that all patients undergoing surgery for pituitary apoplexy be covered with corticosteroids whether they show hypopituitarism preoperatively or not (Uihlein *et al.*, 1957). Postoperative substitution therapy is usually necessary, and this is determined by the patient's endocrine function. It is very uncommon for repeated haemorrhage to occur after the initial operation, but it has been described (Sosman, 1939). Even after early intervention there may be inadequate recovery of visual function. Ocular palsies usually improve rapidly and completely, but visual improvement is slow and less predictable (Walsh and Hoyt, 1969). Postoperatively visual acuity and fields, optic fundi, and the radiographic appearance of the pituitary fossa should be frequently checked.

Pituitary tumours that have undergone haemorrhagic necrosis do not respond well to radiotherapy (Pennybacker, 1961). Furthermore, since this disorder is especially apt to complicate radiotherapy to uncomplicated pituitary tumours (Shepkin, 1955), some authors regard such therapy as being absolutely contraindicated in patients with previous pituitary apoplexy (Schurr, 1966). After decompressive surgery radiotherapy ablation has little place unless regular follow-up shows tumour recrudescence.

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Today's Drugs

With the help of expert contributors we print in this section notes on drugs in common use

Chelating Agents in Medicine

By definition a chelating agent is an organic compound in which two or more electron donor groups, themselves bound by a chemical linkage, co-ordinate with a polyvalent metal, the resultant co-ordination compound having a ring structure. The word chelation is derived from the Greek "che'la," a claw, so describing the way in which the metal is held in organic linkage.

The common donor atoms are nitrogen, oxygen, and sulphur. In practice most chelating agents have one anionic group, from which the metal can displace the hydrogen ion, and one co-ordination linkage, the donor atom sharing a lone pair of electrons with the metal. Metal chelates vary widely in stability depending on the strength of the chelating agent and the chelate-forming ability of the metal.¹ Copper forms the strongest chelates and, given in decreasing order of strength, is followed by nickel, cobalt and zinc, cadmium, iron, manganese, and magnesium. One or more molecules of the chelating agent may be involved in the ring formation; thus copper is bound by two molecules of ethylene diamine:

An example of a naturally occurring agent of considerable biological importance is the porphyrin ring. With magnesium it forms chlorophyll and with iron, similarly bound, it forms haem. The most stable chelate rings are five-membered; as the number of members increases so the stability of the ring decrease. An example of a five-membered ring is that formed by BAL and trivalent arsenic, thus

Some chelates are so stable that the metal can no longer be detected by the most sensitive chemical methods, and this is particularly true if both ligands are co-ordinate linkages.

For a chelating agent to be of use in medicine it must, of course, be non-toxic, be relatively specific for the metal to be bound, be able to form a soluble chelate that will be excreted via the urine or bile, and, preferably, be active when given by mouth. Finally, when formed the chelate must be stable and must be less toxic than the offending metal.

The first chelating agent to be used in clinical medicine was 2,3 dimercaptopropanol (BAL), specifically designed by Peters and his team in Oxford² for treating arsenical war gas poisoning. This was shortly followed by the sodium salt of ethylene diamine tetra-acetic acid (EDTA), which was in-

roduced from industry³ for the treatment of a boy with lead encephalopathy. In 1956 this was in turn followed by penicillamine, dimethyl cysteine, when Walshe⁴ suggested that this compound should be of value for the removal of copper from patients with Wilson's disease. More recently three other chelating agents have been used—diethylene trimine penta-acetic acid (DTPA) and desferrioxamine for the chelation of iron, and, most recently of all, triethylene tetramine as yet another copper-binding agent. Two of these compounds, DTPA and triethylene tetramine, are not at present available for prescription, the former having failed to establish its superiority to other available chelating agents, while the latter has not been available long enough to have undergone critical evaluation.

Dimercaprol

Dimercaprol; BAL; 2,3 dimercaptopropanol is available as a 5% solution in ardis oil containing 10% / benzyl benzoate, each 2 ml ampoule containing 100 mg dimercaprol; this should be administered by deep intramuscular injection together with procaine.

As already mentioned, BAL was specifically designed as an antidote to the arsenical war gas Lewisite, for which it was happily never needed, but it was found to be of value in exfoliative dermatitis in arsenical antisyphilitic therapy. It has also been used for the control of toxicity developing during organic antimony treatment, for the management of reactions to gold therapy, and also for mercury intoxication. Its principal clinical use has probably been for copper chelation in the treatment of Wilson's disease,⁵ but here it has now largely been superseded by penicillamine.⁴

BAL is best administered in short courses in doses of 100 mg; four times on the first day; twice on the second, third, and fourth days; and once only on the fifth and sixth days. It is recommended that BAL should not be used in the presence of liver disease, but in practice it has been used in patients with Wilson's disease and it is the drug of choice for arsenic poisoning, which is also often associated with liver damage. The injections are painful and frequently as-