Pituitary apoplexy (spontaneous pituitary necrosis)

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Summary

Pituitary apoplexy or spontaneous pituitary necrosis is an ill-understood clinical syndrome. It may occur as a neurological emergency requiring urgent interference in a patient with a known pituitary dysfunction or it may be responsible for drawing attention to an as yet unrecognized pituitary pathology. It has a bizarre clinical profile and an unpredictable neurological and endocrine course. Patients may die at once or may recover with or without endocrine/neurological deficit. Six cases of pituitary apoplexy with varied clinical presentation are cited.

Introduction

Pituitary apoplexy commonly presents as a neuro-surgical emergency requiring prompt decompression of the pituitary mass under cortico-steroid cover (Epstein *et al.*, 1971). Spontaneous recovery, however, has been reported even with re-ossification and reduction in the size of the pituitary fossa (Krueger, Unger and Roawit, 1960; Unger and Roawit, 1959; Camp, 1949). The syndrome is characterized by a dramatic onset with severe headache, nausea, vomiting, signs of meningeal irritation, fever, drowsiness, confusion, coma, ocular palsies, amblyopia, cerebrospinal fluid changes and sometimes bizarre neurological deficit. Patients may die within hours or days or may recover, with or without endocrine deficiency, on conservative therapy or with surgery. Six cases of pituitary apoplexy with different clinical presentations are reported.

Materials and methods

Case 1

A 32-year-old female patient, a known case of acromegaly, was treated with external irradiation. Five months later, at 11.30 p.m., she awoke complaining of severe headache and giddiness. She vomited twice, had a generalized tonic spasm and

became unconscious. When brought to hospital she was semi-comatose, had neck rigidity, photophobia and positive Babinski's sign. Fundi were clear; cerebrospinal fluid (CSF) was under tension and showed raised proteins (0.65 g/l) with lymphocytes $0.01 \times 10^9/l$. She was treated conservatively with corticosteroids. She improved in 72 hr and was discharged from hospital. The details of pre- and post-apoplexy endocrine tests are given in Table 1. At present (1980) she is maintained on replacement therapy with thyroxine (0.15 mg daily) and cortisol (20 mg daily) and is doing well. On treatment she is euthyroid and euadrenal although her menses have not yet returned.

Case 2

A 44-year-old woman with acromegalic features and 27 years' secondary amenorrhoea presented in coma which had been preceded by severe headache. She had pale nipples, pyrexia (38°C), signs of meningeal irritation, and no pubic or axillary hair. The fundi and visual fields were normal. The CSF was under increased pressure and contained proteins 0.54 g/l and lymphocytes $0.02 \times 10^9/l$. A skull X-ray showed an enlarged pituitary fossa. A spontaneous infarction of a pituitary tumour was diagnosed. Corticosteroid treatment rapidly improved her condition.

Two years later endocrine assessment showed mild hypothyroidism (protein-bound iodine 244.3 nmol/l), and low plasma cortisol levels (69 nmol/l at 9 a.m.) (Table 2). A standard insulin tolerance test produced hypoglycaemia with a minimum blood sugar concentration of 1.1 mmol/l when the maximum values of plasma cortisol and growth hormone were below normal (88.3 nmol/l and 10.5 µg/l respectively). Growth hormone levels were not suppressed during a standard glucose tolerance test (minimum growth hormone levels were 8.2 µg/l) confirming

TABLE 1. Endocrine function tests. Case 1

(a) Hypothalamic-pituitary-thyroid axis					
Protein bound iodine (nmol/l)		512.2		(181.3)	
Serum thyrotrophin (mu./l)		3.4		(0.1; 1.2; 3.0)	
(b) Hypothalamic-pituitary-adrenal axis					
Plasma cortisol (nmol/l)	9 a.m.	91.1; 172.5		(13.8; 8.3)	
	4 p.m.	63.5		undetectable	
(c) Hypothalamic-pituitary-gonadal axis					
LH (u./l)		6.2		(2.4)	
FSH (u./l)		8.2		(2.6)	
(d) 24-hr GH profile (mean concentration)					
(µg/l)		23.3		(4.7)	
(e) Insulin tolerance test*					
Time (min)	0	30	60	90	120
Blood sugar (mmol/l)	5 (4.4)	1.8 (1.6)	2 (1.7)	3.7 (3.3)	4.7 (3.9)
GH (µg/l)	13.6 (3.7)	23.8 (4.8)	8.8 (4.7)	10.4 (4.9)	16.0 (5.0)
Plasma cortisol (nmol/l)	151.8 (13.8)	77.3 (13.8)	151.8 (13.8)	104.9 (8.3)	77.3 (8.3)
(f) Glucose tolerance tests					
Time (min)	0	30	60	90	120
Blood sugar	5.5 (5)	6.4 (7.2)	5.5 (4.4)	5 (4.2)	5.5 (3.9)
GH (µg/l)	16 (3.9)	13.6 (1.9)	16.4 (4.4)	13.6 (4.6)	9.1 (4.6)

Figures in brackets are post-apoplexy figures.

LH = luteinizing hormone; FSH = follicle-stimulating hormone; GH = growth hormone.

TABLE 2. Endocrine function tests. Case 2

(a) Hypothalamic-pituitary-thyroid axis					
Protein-bound iodine (nmol/l)		61.38			
24-hr radio-iodine uptake		15%			
(b) Hypothalamic-pituitary-adrenal axis					
Plasma cortisol (nmol/l)	9 a.m.	69			
30 min - after 250 µg plain Synacthen test		684.5			
(c) Hypothalamic-pituitary-gonadal axis					
LH u./l		3.6			
FSH u./l		5.4			
(d) Insulin tolerance test					
Time (min)	0	30	60	90	120
Blood sugar (mmol/l)	3.3	1.1	2	2.9	3.2
Plasma cortisol (nmol/l)	77.3	11.0	88.3	66.2	22.1
GH (µg/l)	11	14	10.5	10.0	7.9
(e) Glucose tolerance test					
Time (min)	0	30	60	90	120
Blood sugar (mmol/l)	3.4	6.1	5.1	3.7	4.3
GH (µg/l)	8.2	9.1	10.0	9.4	9.6

LH = luteinizing hormone; FSH = follicle-stimulating hormone; GH = growth hormone.

autonomous growth hormone production by the pituitary tumour. Serum luteinizing hormone was 3.6 u./l and serum follicle stimulating hormone was 5.4 u./l, compared with normal post-menopausal levels of 20 u./l and 12.5 u./l respectively (Table 2). The fundi and visual fields remained normal. L-thyroxine was combined with cortisol therapy and regular follow-up was maintained. Seven years later,

bitemporal hemianopia had developed with further enlargement of the pituitary fossa and irregular destruction of its floor and anterior wall. A huge intrasellar tumour which contained fresh blood and which stretched the optic nerves was removed. Histology showed a pituitary adenoma containing predominantly chromophobe cells with 15-20% acidophilic cells. Post-operative irradiation was given

TABLE 3. Insulin-tolerance test before and after air encephalogram. Case 3

Time (min)	0	30	60	90
Blood sugar (mmol/l)	4 (3.9)	1.7 (1.6)	3.4 (3.8)	3.8 (5)
Plasma cortisol (nmol/l)	552 (66.2)	538.2 (33.1)	690 (33.1)	419.5 (49.7)
Serum growth hormone (μ g/l)	3.8 (1.5)	4.8 (4.3)	6.1 (1.9)	5.1 (1.4)

to avoid recurrence. She is currently (1980) well on replacement therapy and her visual fields have improved.

Case 3

A 26-year-old woman presented with amenorrhoea and galactorrhoea after discontinuing oral contraceptive therapy. Skull X-rays showed an enlarged pituitary fossa, and air encephalography (AEG) was performed to delineate the extent of the tumour. Thirty min after AEG, she developed severe headache, neck rigidity and hypotension. The CSF protein content was 0.9 g/l with lymphocytes 0.13×10^9 /l. She recovered on parenteral corticosteroids. Results of endocrine assessment performed 2 months after AEG showed that the adrenocortical response to hypoglycaemia had disappeared and the growth hormone response remained impaired (Table 3). Cortisol therapy was prescribed and she is currently well although her periods have not restarted.

Case 4

A 32-year-old acromegalic patient was admitted for a detailed endocrine assessment. One day after his admission and before investigations could be initiated he developed sudden severe headache and died within 30 min of onset of symptoms. Post-mortem revealed a fresh haemorrhage with an intrasellar pituitary tumour which was extending up

to and pressing upon the carotid artery and the third cranial nerve.

Case 5

A 60-year-old man reported with a persistent headache. Two days later he was admitted in coma with pyrexia (39°C), neck rigidity, right oculomotor nerve palsy and right hemiplegia. Skull X-rays showed an enlarged pituitary fossa. The CSF was xanthochromic with many red and white cells, the protein content was increased to 2.5 g/l. An intracerebral haemorrhage was diagnosed and treated. He was discharged after a few days. Two years later he presented with progressive lethargy, drowsiness, confusion, and hypotension. PBI was 252 nmol/l; Thyopac-3, 126 and 9 a.m. plasma cortisol 63.5 nmol/l. These investigations confirmed that he had developed pituitary failure. He is currently (1980) well on L-thyroxine and cortisol replacement therapy.

Case 6

A 53-year-old female reported to the Endocrine Unit having had a 'black-out' that morning while out shopping. She felt dizzy, fell down, was helped up, stood still with a support and felt better after a minute or two. She was examined and, except for a radiologically enlarged pituitary fossa, nothing else positive was detected. Her endocrine functions were

TABLE 4. Endocrine function tests. Case 6

(a) Hypothalamic pituitary thyroid axis				
Protein bound iodine (nmol/l)		244.3		
TRH test (200 μ g/i.v.)	Time	0	60	
	TSH			
	(mu./l)	24.6	27.5	24.6
(b) Hypothalamic pituitary adrenal axis				
Plasma cortisol (nmol/l)	9 a.m.	389.2		
(c) Insulin tolerance test				
Time (min)	0	30	45	60
Blood sugar (mmol/l)	4.4	1.5	1.1	1.6
Plasma cortisol (nmol/l)	345	587.9	690	725.9
Growth hormone (μ g/l)	0.5	1.1	9.0	16.6
				12.6

TSH = serum thyrotrophin.

found to be normal. A silent intrasellar growth (?chromophobe adenoma) was suspected. Serum prolactin was not estimated. She was advised to report for review every 6 months. After 18 months she started complaining of temporal headaches which she had not experienced before. She complained of easy fatiguability. Her weight was steady and she had no weather intolerance. She had had her menopause 7 years before. Her vision was normal. Clinical examination revealed soft, thin and easily bruised skin, with sparse body hair. Axillary and pubic hair was very scanty. Temperature, pulse and respiration were normal; BP, 120/80 mmHg; visual fields and fundi were normal; endocrine function tests were as in Table 4. Pneumoencephalogram showed an enlarged sella turcica two-thirds of which were filled with air.

Discussion

Pituitary adenomas are extremely variable in rate, direction and extension of their growth, their effect on health and vision and spontaneous degenerative changes. Chronic degenerative changes take the form of colloid cystic degeneration, reparative fibrosis and calcification. These changes are responsible for the arrest or 'burning out' of activity in a pituitary tumour such as is seen occasionally in acromegaly, as well as the rare development of partial or complete hypopituitarism. Occasionally infarction or haemorrhage with or without infarction occurs in a pituitary tumour and destroys most of the solid tumour, leading to the clinical syndrome of pituitary apoplexy. Once infarction has occurred a large portion of the adenoma or even the entire tumour becomes a haemorrhagic mass that swells rapidly and produces acute compression of the neighbouring structures. It may not only compress the carotid mechanically but it may also induce local vasospasm by irritation. Some blood may escape from it into the basilar sub-arachnoid space or it may set up an inflammatory reaction in the basilar cisterns (List, Williams and Ballyeat, 1952). If the haemorrhagic tumour extends into the suprasellar sub-arachnoid space, it may involve the third cranial nerve and carotid artery and may even compress the hypothalamus, producing a bizarre clinical picture with protean neurological deficits. The basic pathology of spontaneous haemorrhage into a pituitary tumour is not certain, although its close association with radiotherapy is well documented. It may be due to rapid growth of the neoplastic cells which outstrip their vascular supply and produce ischaemic necrosis, or to rupture of the fine-walled vessels in the tumour (Muller and Pia, 1953). Once ischaemic necrosis takes place, the blood vessels lose the support of the surrounding tissue and may give way, leading to haemorrhage. The

tumour swells and becomes a huge haemorrhagic mass beyond the limits of the original adenoma. The haemorrhage in the pituitary tumour sets up a vicious circle in which the blood supply is greatly compromised and the adenoma is totally or partially destroyed. Sufficient tissue may be spared to maintain normal function although this is uncommon.

Bleibtreu in 1905 appears to be the first to have recorded a pituitary haemorrhage. In the post-mortem examination of a 21-year-old acromegalic patient he discovered that the pituitary gland had been replaced by a mass of orange-coloured amorphous material. Dingley in 1932 reported the case of a man who dropped dead after running for a bus, the patient's previous health had been excellent. At post-mortem, a chromophobe adenoma with large fresh haemorrhage was detected. Since then, many reports of pituitary haemorrhage have appeared in the literature, involving both chromophobe and eosinophilic adenomata (Kirshbaum and Chapman, 1948; Broughan, Hausner and Adams, 1960; Locke and Tyler, 1961; Uihlein, Balfour and Donovan, 1957; Wright, Ojemann and Drew, 1965). Broughan *et al.* (1950) termed it 'pituitary apoplexy'.

Endocrine abnormalities in the form of deficiency of gonadotrophin, corticotrophin (ACTH), thyrotrophin (TSH) and growth hormone may result singly or in combination. The pituitary apoplexy in case 1 occurred 5 months after she had completed external radiation to the pituitary. In the second case the necrotic process involved the pituitary stalk impairing the transport of hypothalamic-releasing factors to the anterior pituitary. It is very rare that further growth of pituitary tumour takes place after apparent infarction to the extent of causing restriction of the visual fields, as seen in this case. It is therefore wise to check the visual fields and skull X-ray periodically in patients who have had an infarction or apoplexy of a pituitary tumour. In the third patient, the pituitary apoplexy was precipitated by an air encephalogram. The fourth patient had a dramatic onset leading to sudden and unexpected death in 2 hr. The fifth patient provides an example of the more common clinical problem of pituitary apoplexy, although it is of interest that the clinical features of hypopituitarism did not become apparent for 2 years. In the sixth patient, the empty sella obviously resulted from a silent spontaneous pituitary infarction of the intra-sellar tumour which failed to produce any noticeable symptoms at the time.

Conclusion

The onset of pituitary apoplexy is usually sudden and dramatic with typical symptomatology. The confirmatory triad consists of evidence of pituitary dysfunction, enlarged pituitary fossa; abnormal

CSF, and haemorrhagic necrotic tumour on operation. Surgical decompression under corticosteroid cover is the only sure hope of saving the vision. Conservative management may help but is not the ideal treatment. Frequent periodic assessment in follow-up is obligatory.

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