Pituitary apoplexy associated with a triple bolus test

Case report

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The authors report a case of pituitary apoplexy resulting in bilateral internal carotid artery occlusion, with marked depression of consciousness and hemiplegia. After transsphenoidal tumor decompression, restoration of flow in both carotid arteries was documented angiographically and the patient made an excellent clinical recovery. The unique aspect of this case is that the pituitary apoplexy was apparently precipitated by neuroendocrine manipulation, performed as a preoperative test of pituitary function.

KEY WORDS • pituitary apoplexy • vascular occlusion • triple bolus test • transsphenoidal surgery • carotid occlusion • pituitary function

Pituitary apoplexy is the clinical syndrome observed when infarction and/or hemorrhage in a preexisting pituitary adenoma results in acute swelling of the tumor and compression of adjacent structures. First recognized in 1905 by Bleibtreu, it is characterized by the sudden onset of headache, visual impairment, extraocular muscle palsies, and disturbance of consciousness. Signs of focal cerebral hemispheric dysfunction are uncommon.

The authors report a case of pituitary apoplexy temporally related to a “triple bolus” endocrinological test, and resulting in marked alteration in consciousness and hemiplegia. Bilateral occlusion of the intracavernous internal carotid artery (ICA) was found on angiography. The neurological and neuroradiological findings were reversed following emergency transsphenoidal surgery.

Case Report

This 48-year-old left-handed man presented with a 2-year history of diminished sight in his left eye. A visual field defect was detected and he was referred to the neurosurgical service of the Toronto General Hospital. He was otherwise asymptomatic. Physical examination revealed incongruous bitemporal hemianopsia, with no light perception in the left temporal field and altered color perception in the superior temporal quadrant of the right eye. There was a left relative afferent pupillary defect and pallor of the temporal margin of the left optic disc. Visual acuity was 20/80 in the left eye and 20/20 in the right. Extraocular movements were normal. There were no cranial bruits and the remainder of the neurological and general physical examination was normal.

Skull x-ray films revealed gross expansion of the sella with destruction of the dorsum and floor. Sellar tomography demonstrated soft-tissue extension into the sphenoid sinus. Venous subtraction angiography revealed patent but compressed intracavernous ICA’s bilaterally, and elevation of the A1 and A2 segments of the anterior cerebral arteries, with no evidence of aneurysm (Fig. 1). As part of the preoperative endocrine evaluation, a “triple bolus” test was performed. This test involves the intravenous injection of 100 μg luteinizing hormone-releasing hormone, 200 μg thyrotropin-releasing hormone (TRH), and 0.1 units/kg regular insulin.

Five minutes after the bolus injection, the patient complained of sudden severe bifrontal headache and blurring of vision. Ten minutes later, he complained of numbness in his right arm. Twenty minutes following the bolus, the blood glucose level was determined to be 33 mg%. The patient then suddenly began to sweat profusely, vomited, and was unable to give any verbal response to questioning. Blood pressure was 140/
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80 mm Hg. A bolus injection of 50% glucose was given. Gross left hemiparesis became evident and the patient became increasingly obtunded. Blood glucose was determined then to be 166 mg%. The patient remained normotensive with a supple neck. Roving eye movements were noted without evidence of extraocular palsy, but there was a tendency to look to the right. Immediate computerized tomography revealed a non-enhancing soft-tissue mass of relatively uniform density expanding the sella, without evidence of hemorrhage (Fig. 2). Cerebral arteriography was immediately performed and revealed occlusion of both ICA's at the level of the cavernous sinus (Fig. 3).

Operation. The patient, unresponsive to commands, was taken to the operating room where a trans-sphenoidal removal of the pituitary tumor was carried out. A large soft-tissue mass was encountered in the sphenoid sinus and, when its capsule was incised, necrotic-appearing material under tension issued forth. Gross removal of tumor was carried out. The total elapsed time between the onset of the patient's ictus and the removal of the tumor was approximately 8½ hours.

Postoperative Course. Immediate postoperative angiography documented patency of both ICA's (Fig. 4). The patient was initially aphasic, with left hemiplegia, and blind in the left eye. Subsequently, both speech and

FIG. 2. Plain computerized tomography scan showing an isodense mass within the sella (left) which rises above and encroaches on the suprasellar cistern (right, arrows).

FIG. 3. Preoperative right common carotid angiogram (left) and left common carotid angiogram (center) showing compression of the parasellar internal carotid arteries (complete on the right and severe on the left). The only intracranial flow is via the small posterior communicating vessels seen on the preoperative vertebral angiogram (right).
power returned to normal; visual acuity was 20/20 in the right eye and finger-counting in the left. Visual field defects remained similar to those on admission. No extraocular paresis was ever noted. The patient was discharged home on the 10th postoperative day. At 6 months postoperatively, the patient was driving his car and had returned to full employment. Visual acuity was 20/20 on the right side and 20/300 on the left.

Pathological Examination. Microscopic examination of the surgical specimen revealed a chromophobe adenoma that had recently been almost totally infarcted (Fig. 5). On the basis of the histological appearance, the age of the infarct could not be precisely determined. The changes, consisting of eosinophilia of cytoplasm and pyknosis of nuclei seen in tumor cells, might have developed in a period as short as 9 hours but might represent older infarct (up to 24 to 48 hours old).

Discussion

Pituitary apoplexy is an uncommon complication of pituitary adenoma. Although up to 16.6% of all pituitary tumors removed surgically show histological evidence of infarction, only 6.8% of all patients with pituitary adenomas develop the clinical manifestations of pituitary apoplexy. Most cases occur spontaneously; however, many factors have been associated with pituitary apoplexy, including bromocriptine therapy, estrogen treatment, radiation therapy of pituitary tumors, head trauma, anticoagulant therapy, pregnancy, arteriography, cerebral aneurysms, lumbar puncture, myelography, pneumoencephalography, increased intracranial pressure, and nasal catarrh.

Pituitary tumors may be prone to infarction because of the local vascular anatomy. The pars distalis of the anterior lobe derives its blood supply exclusively from the hypophyseal-portal capillary network originating from anastomoses between the superior and inferior hypophyseal arteries, both of which are branches of the ICA. The pars distalis receives little if any blood supply directly from arteries, and is dependent on the portal blood supply arising within the infundibulum. Expansion of the sellar contents due to an enlarging pituitary adenoma may cause occlusion of the blood supply, particularly in the region of the diaphragmatic notch where the hypophyseal-portal network lies in close approximation to the pituitary stalk. The resulting ischemia of the anterior lobe and tumor causes swelling of the sellar contents, and the acute signs of pituitary apoplexy ensue. The role of the various associated factors in the pathogenesis of pituitary tumor infarction is not well understood; presumably they contribute to acute deterioration of an already compromised tumor blood supply.

Signs of focal cerebral hemispheric dysfunction are uncommon in pituitary apoplexy. Hemiplegia as one of the presenting signs is unusual, but has been described in a number of reports. The mechanism has been postulated to be cerebral ischemia resulting from spasm, hypotension, or mechanical obstruction of a large artery by an enlarging mass. The most unique and interesting aspect of our case is the apparent precipitation of pituitary apoplexy by the triple bolus test. To our knowledge, this has not been previously reported.

Two major related questions arise which are crucial...
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Fig. 5. Photomicrograph of a section of chromophobe adenoma of the pituitary gland. There is a fragment of viable tumor on the top, and recent infarction below is characterized by pyknosis of tumor-cell nuclei. The absence of any inflammatory reaction is in keeping with an infarction age of a few hours. H & E, × 20.

to the interpretation of the clinical and radiological findings and the role of the triple bolus test in the pathogenesis of the pituitary apoplexy in this case. These concern the nature of the occlusion of the carotid arteries, and whether the infarction of the pituitary adenoma was spontaneous and coincidental with the triple bolus or was precipitated by the injection.

If occlusion of the carotid arteries was due to compression by the pituitary adenoma, then infarction must have occurred at some time prior to the triple bolus injection, since, in the absence of hemorrhage, swelling of infarcted tissue would be expected to take at least several hours to occur. If on the other hand the carotid occlusions were due to vasospasm, then both arterial spasm and tumor infarction might be attributed to the triple bolus injection. Unfortunately, the issue cannot be resolved by the histology of the infarcted tumor since there are no reliable criteria to distinguish infarction of 9 hours from that of 24 hours duration, for example. While the angiographic appearance immediately preoperatively is also less than conclusive, vascular patency was immediately restored following tumor decompression.

The effect of the components of a triple bolus test on the cerebral vasculature has only recently been investigated. Insulin-induced hypoglycemia has been shown to have no effect on cerebral blood flow (CBF) in cats. However, in rats, CBF is significantly reduced by hypoglycemia with residual damage related to arterial insufficiency, and not due to prolonged substrate deficiency. In our patient, hypoglycemia was probably not a factor in his pituitary infarction for several reasons. First, the hypoglycemia was not severe; Second, the hypoglycemia was rapidly detected and corrected. Finally, the patient's initial symptoms occurred during the injection of insulin, well before any significant hypoglycemia could possibly have occurred. Counter-regulatory hormone release (specifically, epinephrine and norepinephrine) in response to insulin-induced hypoglycemia theoretically may have had an effect on cerebrovascular supply in this patient. However, there are currently no animal or human studies that clearly delineate this phenomenon. Another possibility for the acute pituitary gland infarction in this patient may be the recently described direct effect of insulin upon smooth-muscle tone in isolated rat uterine fibers. In a glucose-free medium, insulin was found to enhance smooth-muscle tone. This effect was abolished when verapamil was incubated with the fibers. The obvious implication is that insulin may directly affect vascular smooth-muscle tone by modulation of calcium transport.

Thyrotropin-releasing hormone has many clinically documented adverse effects, including nausea, metallic taste, a feeling of urinary urgency, light headedness and headaches, abdominal and chest discomfort, pleasurable genital sensation, bronchospasm, elevated blood pressure, loss of consciousness, and asystole. It has been shown that TRH elevates serum levels of norepinephrine and this may, in fact, explain most of the documented side effects. There has been no study examining the effect of TRH on CBF. The possibility that TRH-induced vasospasm may have precipitated the pituitary gland infarction in this patient must be seriously considered, especially in light of the rapid onset of symptoms and subsequent course of events.

Gonadotropin-releasing hormone (GnRH) has not had documented acute effects on cerebral or peripheral circulation. Although it is less likely to be associated with the pituitary infarction in this patient, GnRH must also be considered as a possible cause. Other etiologies to be considered include a synergistic effect of any two or all three components of the triple bolus test. Although the possibility that pituitary apoplexy occurred spontaneously and coincidentally with the test cannot be excluded, this seems unlikely.

In summary, sudden infarction of a pituitary macroadenoma with subsequent impairment of cerebral hemispheric circulation occurred in a man undergoing a routine triple bolus test for preoperative assessment of pituitary gland function. The exact etiology of the ictus in this patient is not clear. The temporal course and coincidence with the triple bolus test suggests that the cerebral event was not merely spontaneous but instead may have been precipitated by vasospasm induced by TRH or by catecholamine response to hypoglycemia, or both. It might be argued that some degree of arterial compression did exist prior to the triple bolus injection secondary to growth of tumor laterally into cavernous sinuses and that such compression might render the arteries unusually susceptible to vasospasm. This would account for the possible occurrence of vasospasm in this case despite its rarity as a complication of the triple bolus test.

In light of the present case, the advisability of routine preoperative assessment of pituitary endocrine function with a triple bolus test in a patient with a pituitary...
macroadenoma should be called into question. The perioperative management of such patients (with intra-
venuous corticosteroids) is usually carried out independ-ently of the results of the test. The results can often
take weeks to return, and usually have no bearing upon
the patient’s postoperative endocrinological status. Se-
rious consideration of potential risks versus benefits
must precede the administration of the triple bolus test
to such patients. Pituitary apoplexy should be recog-
nized as a possible complication of the triple bolus test,
especially in patients with large pituitary tumors.

Cranietomy has been the standard method of surgi-
cal treatment; however, more recently the transsphe-
noidal approach has been recommended as the proce-
dure of choice in this condition.7 Regardless of the
approach, early diagnosis and immediate decompres-
sion is necessary if vision is to be spared and permanent
ischemic deficits prevented.

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