Pituitary Apoplexy: The Role of Atheromatous Emboli

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Abstract:

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Patients with clinically unsuspected pituitary adenomas may present with sudden severe frontal headaches, stupor, ophthalmoplegia, meningeal irritation, compression of the optic nerves or chiasm, and abnormal cerebrospinal fluid. These findings are commonly misinterpreted as due to a ruptured cerebral aneurysm. The clinical features and controversial pathogenic mechanisms of pituitary apoplexy are reviewed. An unusual case of pituitary apoplexy with many atheromatous emboli in the tumor is presented. This previously undescribed possible cause of pituitary apoplexy should be considered in older patients with known predisposing factors for systemic atheromatous embolism.

Introduction

Since the first report of pituitary apoplexy by Bleibtreu in 1905, a variety of mechanisms have been proposed to explain this vascular catastrophe occurring predominantly in pituitary adenomas. We report a case of pituitary apoplexy in which a previously undescribed factor, atheromatous emboli, must be strongly considered as an etiological agent.

Case Report

A 69-year-old white male (NYH 90-36-35) was admitted to The New York Hospital three days antemortem with a one-day history of severe bifrontal headache, ptosis of the right eye, and vomiting.

One month antemortem, the patient was admitted for evaluation of severe peripheral vascular disease. X-rays showed extensive calcification of the aorta and its major abdominal and pelvic branches, vessels of the extremities, coronary arteries, and aortic valve. A left carotid bruit, decreased peripheral pulses, and trophic lower extremity skin changes were noted. Funduscopical examination showed bilateral arteriovenous nicking. Neurological examination revealed marked limitation of neck motion due to cervical osteoarthritis, decreased deep tendon reflexes, slightly depressed vibratory and pinprick sensation in the lower extremities, a left Babinski sign, bradykinesia, unsteady, slightly broad-based, shuffling gait, and decreased mentation. Visual fields were intact. Cranial nerve function was normal. Skull x-rays showed an intact sella turcica and calcification of the carotid siphons. Serologic reactions for syphilis were negative. Laennec's cirrhosis with hepatomegaly was noted. Atrial fibrillation was attributed to digitalis toxicity. Hypertension (blood pressure 200/95 mm Hg), noted since 1956, was treated with Aldomet.

Three days antemortem, the patient was admitted alert and oriented. Blood pressure was 210/95 mm Hg. Right eye movement was limited to lateral gaze. The right pupil was 6 mm in diameter and fixed. The left pupil was 3 mm in diameter and reactive. Optic disks were flat. Visual fields were intact to confrontation. Meningism was not present. Laboratory data were within normal limits. Two days antemortem, confusion, lethargy, incontinence, marked nuchal rigidity, fever (40.5°C) and a nonreactive left pupil were noted. Lumbar puncture showed an opening pressure of 150 mm H₂O, xanthochromic, benzidine-positive cerebrospinal fluid with 4,350 red blood cells per cubic millimeter, 400 white blood cells per cubic millimeter, with 65% neutrophils and 35% mononuclear cells, sugar 70 mg % (blood sugar 120 mg %), protein 117 mg %, an equivocal gram stain, and negative bacterial cultures. Treatment with mannitol, steroids, and penicillin was begun. The patient continued to deteriorate with progressive obtundation and hypotension. Doll's eyes were lost and corneal reflexes were depressed bilaterally, greater on the right than the left side. The patient had a cardiorespiratory arrest and no resuscitation was attempted. The final clinical diagnosis was subarachnoid hemorrhage secondary to a ruptured right posterior communicating artery aneurysm.

Autopsy Findings

There was severe calcific atherosclerosis of the aorta and its major branches. Numerous ulcerated atheromatous plaques covered by thrombotic material were present in the aortic arch, ostia of the right brachiocephalic and left common carotid arteries, and the abdominal aorta. Other findings included occlusive atherosclerosis of the coronary arteries with an old myocardial infarct, hypertrophy of the heart, marked calcification of the aortic and mitral valve rings, two small papillary tumors near the nodules of Arantius of the aortic valve, arterial and arteriolar nephrosclerosis with old renal infarcts, and severe atherosclerosis of the branches of the circle of Willis with a small cystic infarct in the right putamen. There were also micronodular cirrhosis of the liver, multiple superficial gastric and duodenal ulcers with massive gastrointestinal hemorrhage, mild demyelination of
PITUITARY APOPLEXY

Peripheral nerves of the lower extremities, centrilobular emphysema, and nodular hyperplasia of the adrenal glands. Microscopically, there were atheromatous emboli in the kidneys (fig. 1), adrenal glands, and brain (fig. 2).

The sella turcica was filled with a 1.5 X 2.0 cm hemorrhagic tumor mass which bulged above the diaphragma sellae, eroded the anterior clinoid processes, and markedly thinned the floor of the sella (fig. 3). There was marked lateral extension of the tumor, especially on the right side, with compression of the cavernous sinuses and extension to the carotid artery adventitia. The tumor compressed the optic nerves, optic chiasm, optic tracts, and right oculomotor and trochlear nerves. There was a grayish zone of softening in the central chiasm. The infundibular stalk and adjacent meninges were hemorrhagic. Microscopically, the tumor was a hemorrhagic, largely necrotic chromophobe adenoma. Sections of the tumor showed small vessels including arteries and arterioles filled with acicular clefts, which are the negative image of the cholesterol crystals from atheromatous emboli dissolved by the histological processing fluids (fig. 4). No inflammatory cell reaction to the cholesterol emboli or intravascular fragments of calcific material were seen. There was a sharply demarcated area of acute necrosis in the central portion of the optic chiasm. Small arteries at the junction of the pituitary adenoma and the compressed cavernous sinuses, presumably branches of the superior hypophyseal group or meningohypophyseal trunk, and the carotid siphons, showed marked luminal narrowing by fibrointimal proliferation and calcified atheromata. Intramural hemorrhage, focal necrosis, and neutrophilic infiltration were seen in a medium-sized artery adjacent to the adenoma on the right side. There was hemorrhage, more extensive on the right side, in and around the nerves in the cavernous sinus.

Discussion

Pituitary apoplexy is probably more frequent than the number of reported cases would suggest. A lack of familiarity with the manifestations of this condition leads to its infrequent clinical diagnosis, as in this case. Although there are only approximately 200 reported cases of pituitary apoplexy and Nurnberger and Korey did not find a single example in a series of 117 consecutive pituitary tumors, the actual incidence is probably more accurately reflected in the Lahey Clinic experience reported by Poppen. He noted a 10% incidence of "apoplexy and hemorrhagic..."
Intracerebral artery containing an organized atheromatous embolus. (Hematoxylin-eosin, X 200)

Superior surface of hemorrhagic and infarcted chromophobe adenoma of the pituitary.
necrosis" in a series of 360 pituitary adenomas. Also, degenerative changes including cyst formation and focal fibrosis with hemosiderin-laden macrophages are a frequent incidental finding and presumably are due to some ischemic insult to the pituitary.

The first indication of a pituitary tumor may be the apoplectic episode characterized by sudden, primarily bifrontal headaches, meningeal irritation, impairment of the visual apparatus, ophthalmoplegia, and stupor. Symptoms may progress over the course of weeks or seconds, or sudden death may occur without any symptoms, as in the case reported by Dingley. Sudden lateral expansion of the adenoma may cause a cavernous sinus syndrome. As is true with pituitary tumors in general, oculomotor nerve palsy is more frequent than involvement of the abducens nerve.

Hyperpyrexia may be present. Skull x-rays usually demonstrate changes consistent with a pituitary tumor, but the sella may not be enlarged as was true in our case. Signs of meningeal irritation correlate with the presence of xanthochromic or bloody cerebrospinal fluid. Elevated cerebrospinal fluid protein may be seen. CSF sugar and white blood cell counts are usually normal, but findings similar to meningitis may be seen if the capsule of the tumor ruptures with the release of necrotic material and blood into the cerebrospinal fluid.

Pituitary apoplexy occurs in all age groups, although the mean age is approximately 50 years old. Both sexes are affected with this condition. Pituitary apoplexy seems to occur with a relatively increased incidence in functioning eosinophilic adenomas. However, since approximately 80% of pituitary tumors are chromophobe adenomas, the majority of cases of pituitary apoplexy occur in patients with this lesion. Apoplexy is very rare in basophilic adenomas, probably because a majority of these are microscopic.

The adenomas show variable degrees of hemorrhage and necrosis. The degree of necrosis may be sufficient to cause regression of acromegaly with subsequent recalcification of the sella turcica as in a case reported by Dawson and Kothandaram. Occasionally the apoplectic episode will be followed by
diabetes insipidus or a spontaneous Houssay phenomenon. Symptoms of secondary adrenal insufficiency may predominate acutely, but if the patient survives the catastrophic event, gonadotrophic and thyrotrophic secretion are usually disturbed to a greater degree than corticotrophic secretion.

The most important differential diagnosis is with a ruptured cerebral aneurysm. A "ballooned" sella turcica on skull x-ray, prior endocrinopathy, and the presence of bilateral oculomotor defects support a diagnosis of pituitary apoplexy, but none are pathognomonic. Angiographical studies often resolve the problem. Other conditions which may produce similar signs and symptoms include uncal herniation without compromising pituitary circulation, cerebrovascular occlusions, especially basilar artery disease producing mesencephalic infarction, infectious or degenerative diseases involving the midbrain and diencephalon, and acute retrobulbar neuritis.

Angioembolization,16 radiation therapy,16 trauma,17 and high dose estrogens have been implicated in the development of pituitary apoplexy. However, in the majority of cases, no extrinsic factor can be identified. Brougham et al. proposed that the tumor outgrows its blood supply because of sudden growth with resultant ischemia, necrosis, and hemorrhage. Possible increased fragility of thin-walled blood vessels within the adenoma was suggested by Miller and Pia.19 Tumor growth by itself within a confined space may result in increased pressure on blood vessels. Lateral extension of the tumor may compromise the cavernous sinuses. Dawson and Kothandaram have proposed that in this situation, coughing or sneezing may increase cavernous sinus tension, causing an increased venous back pressure with resultant compromise of arterial circulation. Thrombosis of hypophyseal portal veins has been noted in cases of pituitary apoplexy, and Daniel and Prichard experimentally produced anterior pituitary necrosis in the rat by cauterizing hypophyseal portal vessels. Rovit and Fein theorized that the initiating event in pituitary apoplexy was the impairment of infundibular circulation by impaction of tumor at the diaphragmatic notch. This latter explanation is consistent with the arterial supply of the normal pituitary as described by Xuereb et al.21 However, recent angiographical studies by Baker and Roth et al. have indicated that pituitary adenomas may receive a direct arterial supply via capsular arteries arising as branches of the meningohypophyseal trunk. Circulation from these abnormal vessels would probably not be impaired by impaction of the tumor at the diaphragmatic notch. This latter explanation is consistent with the arterial supply of the normal pituitary as described by Xuereb et al.21 However, recent angiographical studies by Baker and Roth et al. have indicated that pituitary adenomas may receive a direct arterial supply via capsular arteries arising as branches of the meningohypophyseal trunk. Circulation from these abnormal vessels would probably not be impaired by impaction of the tumor at the diaphragmatic notch. In addition, the diaphragma sellae is an extremely variable structure and in many cases a large opening may allow prominent suprasellar extension of tumor without compromising pituitary circulation.

In this case, there was evidence of systemic atheromatous embolization from a markedly atherosclerotic aorta and its major branches. Numerous acicular clefs, typical of dissolved cholesterol crystals from atheromatous emboli, were seen in small arteries of the kidneys, adrenal glands, brain, and the chromophobe adenoma. This patient is typical of those with atheromatous emboli to the central nervous system as reported by Soloway and Aronson. Characteristic features include older age (mean 72.5), hypertension, diabetes mellitus, severe atherosclerosis of the aorta and carotid arteries, and occlusive atherosclerosis of the coronary arteries with old or recent myocardial infarcts. Syphilitic aortitis with aneurysmal dilatation of the ascending aorta may be present. Funduscopical examination often reveals "bright plaques" in retinal arterioles. These correlate with atheromatous emboli and episodes of transient blindness. Atheromatous emboli to the brain tend to lodge in terminal, circumferential branches of the basivertebal and carotid artery systems, with an internal diameter of less than 100 μ. There is relative sparing of midline structures. We were unable to find any reported cases of atheromatous emboli in the pituitary, but there is little reason to suspect that the pituitary would be spared by a process that commonly involves multiple organs, as it did in our case.

We propose that in our case, large numbers of atheromatous emboli resulted in hemorrhagic necrosis of the chromophobe adenoma and the apoplectic syndrome. If the blood supply of the tumor was similar to that seen in the normal anterior pituitary, then atheromatous emboli would decrease the hypophyseal portal circulation and, in turn, cause ischemic necrosis and hemorrhage as described in the experimental model of Daniel and Prichard. If the chromophobe adenoma received a direct arterial supply via capsular branches of the meningohypophyseal trunk, then cholesterol emboli could produce direct ischemia and hemorrhagic necrosis. In either mechanism, the blood supply of the adenoma would already have been compromised by severe atherosclerosis of the carotid arteries and their hypophyseal branches. Since almost all the cholesterol clefs were within vascular lumina of the pituitary adenoma, systemic atheromatous emboli were demonstrated, and the interval between onset of apoplexy and death was short, it seems almost certain that the cholesterol clefs in the pituitary adenoma were the result of atheromatous emboli, rather than due to degenerative changes within the adenoma. Many cases of pituitary apoplexy occur in younger patients who would not be expected to have significant atherosclerotic cardiovascular disease. Therefore, atheromatous emboli would only be a possible explanation of pituitary apoplexy in older patients, especially those with known carotid or aortic atherosclerosis, syphilitic aortitis, hypertension, diabetes mellitus, and transient ischemic attacks. Individual cases of pituitary apoplexy are probably
caused by different mechanisms, one of which may be atheromatous emboli.

References
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