Apoplexy of pituitary adenomas: the perfect storm

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OBJECT Pituitary adenomas occasionally undergo infarction, apoplexy, which often destroys much of the tumor. It is well known that apoplexy can be precipitated by several acute factors, including cardiac surgery, other types of surgery, trauma, insulin infusion, and stimulation with administration of hypothalamic releasing factors.

METHODS The prior focus on mechanisms underlying pituitary apoplexy has been on these acute events. Less attention has been given to the endogenous features of pituitary tumors that make them susceptible to spontaneous infarction, despite that most pituitary apoplexy occurs in the absence of a recognized precipitating event. The authors examine intrinsic features of pituitary adenomas that render them vulnerable to apoplexy—features such as high metabolic demand, paucity of angiogenesis, and sparse vascularity, qualities that have previously not been linked with apoplexy—and argue that it is these features of adenomas that underlie their susceptibility to spontaneous infarction. The sensitivity of freshly cultured pituitary adenomas to hypoglycemia is assessed.

RESULTS Adenomas have high metabolic demand, limited angiogenesis, and reduced vessel density compared with the normal gland. Pituitary adenoma cells do not survive in the presence of reduced or absent concentrations of glucose.

CONCLUSIONS The authors propose that the frequent ischemic infarction of pituitary adenomas is the product of intrinsic features of these tumors. These endogenous qualities create a tenuous balance between high metabolic demand and marginal tissue perfusion. Thus, the tumor is vulnerable to spontaneous infarction or to acute ischemia by any event that acutely alters the balance between tumor perfusion and tumor metabolism, events such as acute systemic hypotension, abruptly decreased supply of nutrients, hypoglycemia with insulin administration, or increase in the tumor's metabolic demand due to administration of hypothalamic releasing factors. It may be possible to take advantage of these intrinsic features of pituitary adenomas by using aspects of this vulnerability for development of new approaches for treatment.

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KEY WORDS pituitary adenoma; pituitary apoplexy; pituitary surgery

PITUITARY tumors spontaneously infarct at a relatively high rate, higher than any other CNS tumor. This occurs with or without hemorrhage. The typical clinical entity was described relatively late, in 1950, by Brougham et al.¹² Since then pituitary apoplexy has been the subject of many reports describing the clinical presentation, patient management, imaging features, and outcome, as well as reports of acute circumstances predisposing to its occurrence.^{9,10,14,15,17,22–25,29,32,36,37,39,45} We propose here that infarction of these tumors is the product of a combination of intrinsic features of these tumors and

that it is the tenuous imbalance between their high rate of demand for nutrients combined with their limited intrinsic blood supply that makes them vulnerable to infarction, with or without precipitating events, and suggest that this circumstance may permit new approaches to treatment based on this peculiar vulnerability.

Case of Pituitary Apoplexy

A 57-year-old male had the sudden onset of headache followed by excessive thirst, polydipsia, loss of energy, and

ABBREVIATIONS FDG = fluorodeoxyglucose; PET = positron emission tomography; VEGF = vascular endothelial growth factor.

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generalized weakness. Pituitary MRI performed 4 days after the onset of his symptoms demonstrated findings consistent with apoplexy of a pituitary macroadenoma (Fig. 1 left). Endocrine testing demonstrated panhypopituitarism. He was treated with glucocorticoids and without surgery. On MRI 5 months later (Fig. 1 right) there was no evidence of residual tumor.

Arguments Supporting the Proposed Mechanism

Pituitary Tumors Have High Energy Demand/Consumption

The whole-body [^{18}F]-fluorodeoxyglucose (FDG)-positron emission tomography (PET) and pituitary MR images shown in Fig. 2 were obtained in a 62-year-old man in whom mediastinal lymphadenopathy was being investigated. The images demonstrate a pituitary macroadenoma that was not causing symptoms. Assessment indicated that this was a nonfunctioning pituitary adenoma.

The introduction of clinical PET and the frequent use of FDG to study tumors and their metabolism demonstrated that pituitary adenomas consume a large amount of glucose in comparison with the surrounding brain, uptake exceeding that which occurs with other benign CNS tumors.^{4,5,13,16,33} Further, using PET Muhr et al., and others, demonstrated consistent high uptake of [^{11}C]-L-methionine by pituitary adenomas of various types.^{6,26} This high uptake of these metabolic tracers occurs with micro- and macroadenomas as well as secretory and nonfunctioning tumors.¹⁶ In contrast, the normal pituitary is not visualized as a region of increased uptake on FDG-PET.¹⁶ This elevated demand for glucose and methionine in pituitary adenomas is reduced by therapies that alter the tumor's hormone secretion (medical therapy with agonists of dopamine or somatostatin)^{4,6,16,26} or viability (radiation therapy).¹⁶

Pituitary Tumors Have Limited Expression of Angiogenic Factors, Reduced Density of Vascularity, Limited Blood Supply, and Increased Intratumoral Pressure

Pituitary tumors have limited blood supply compared with other types of primary CNS tumors. This was recognized in the era in which arteriography was commonly used to assess patients with pituitary tumors. Pituitary adenomas show no "blush" on cerebral arteriography; in most instances they have no visible blood supply detectable with arteriography. It had been noted even before the introduction of arteriography that at surgery pituitary macroadenomas tended to be relatively avascular compared with other types of CNS tumors. With the introduction of contrast-enhanced MRI it became apparent that these tumors almost universally have reduced contrast enhancement compared with the normal gland, which is consistently seen as a brightly enhancing tissue relative to the limited enhancement of the adjacent pituitary tumor (Fig. 2C). Further, the introduction of dynamic-enhanced imaging permits visualization of the blood flow to the pituitary gland and the tumor; it clearly and consistently demonstrates earlier and greater blood flow to the pituitary gland than to the tumor.

FIG. 1. Left: Anteroposterior view T1-weighted MR image with contrast obtained 4 days after the onset of symptoms of pituitary apoplexy in a 57-year-old man. Right: Anteroposterior view T1-weighted MR image with contrast obtained 5 months later showing no evidence of residual tumor.

In our study of vascular endothelial growth factor (VEGF) expression by various types of CNS tumors using an RNase protection assay, we examined 10 pituitary adenomas (4 Cushing's disease and 1 Nelson's corticotroph adenoma, 3 somatotroph adenomas, 1 thyrotrophin-secreting adenoma, and 1 nonsecreting adenoma). We found increased expression of VEGF mRNA compared with normal brain in only 2 of the 10 pituitary tumors.⁷ In fact, in the pituitary adenomas the mean level of VEGF mRNA expression detected by RNase protection assay was similar to the negligible level expressed by normal brain.

Consistent with this is reduced angiogenesis in pituitary tumors.^{18,34,40} This reduced density of microvasculature appears to have been first noted by Schechter³⁴ and was later confirmed in a series of studies using special stains by Turner et al., who examined the microvessel density of pituitary tumors by counting vessels labeled with endothelial markers (using antibodies to CD31, factor VIII-related antigen, and biotinylated *Ulex europaeus*).⁴¹ Schechter, Jugenburg et al., and Turner et al. all observed less dense vessel representation in pituitary tumors than in the normal pituitary;^{18,34,41} this is distinctly different from other tumor types that have been studied similarly.^{11,18,40,42,43} For instance, in contrast to the circumstance with pituitary tumors, benign and precancerous lesions of the breast have a greater density of microvasculature than the normal host tissue.¹¹

Thus, available evidence indicates that there is limited angiogenesis and reduced vessel density in pituitary adenomas, features upon which excess pressure might act to further diminish perfusion of the adenoma.

Available evidence indicates high intratumoral pressure in large and small adenomas. At surgery, high intrasellar pressure (20–40 mm Hg) has been measured consistently in patients with pituitary macroadenomas.^{1,19–21} Measurement of blood flow in pituitary tumors versus normal gland using the xenon washout technique during surgery demonstrates very low blood flow in the tumor compared with the normal gland.¹⁹ Further, the development of a histological pseudocapsule, a result of the effect of increased pressure within an adenoma on the surrounding normal pituitary gland, begins to occur with tumors as small as 1–2 mm and occurs in essentially all micro- and macroadenomas.²⁷ This increased pressure within an adenoma, combined with intrinsically limited vascularity, reduces the perfusion of the tumor and enhances the susceptibility of it to ischemia and to infarction and occurs in large and small tumors (see below).^{24,28,37}

FIG. 2. This 62-year-old man had a CT FDG-PET performed as a screening test. It revealed an incidentally discovered pituitary macroadenoma. Sagittal whole-body view (A) and axial cranial view (B) of the CT FDG-PET show exuberant uptake of FDG in the small macroadenoma. Pituitary MR images obtained after contrast administration are shown in the anteroposterior (C) and sagittal (D) views. The arrow indicates the normal gland which has been displaced to the far left side of the sella by the tumor.

Circumstances Precipitating Apoplexy of Pituitary Adenomas

Several clinical situations have long been known to be associated with induction of apoplexy of pituitary adenomas. These include events that acutely diminish blood pressure or plasma glucose and events that increase tumor metabolism and demand for blood flow.

The most common circumstances that acutely precipitate pituitary apoplexy are events that alter systemic blood pressure, such as cardiac surgery and myocardial infarction.^{2,10,15,25,35,38} Traumatic injury associated with shock, aortic dissection, and other types of surgery have also been linked with the onset of pituitary apoplexy.^{10,35,37,39,45}

Events that alter the balance between glucose supply and metabolic demand, such as hypoglycemia associated with insulin tolerance testing, or increasing metabolic demand by stimulation testing with hypothalamic releasing factors, have been reported to precipitate apoplexy of pituitary tumors.^{8,10,31,44,46}

Experiments to Assess Vulnerability of Pituitary Tumor Cells to Hypoglycemia

To examine the tolerance of fresh pituitary tumor cells to glucose deprivation compared with normal cells we performed the following experiments.

Pituitary tumors for laboratory investigation were obtained under an NINDS institutional review board–ap-

proved protocol. Pituitary tumor cell cultures (from 1 ACTH-secreting, 1 growth hormone–secreting, and 1 non-secreting tumor) were prepared by enzymatic digestion as previously described³⁰ with minor modifications. Red blood cells were removed by subjecting the cell suspension to lymphocyte separation medium. Tumor cells were cultured in DMEM-10% FCS for 24 hours. Tumor cells were then plated in serum-free medium with or without glucose for 20 hours. In 3 of 3 freshly prepared cultures, pituitary tumor cells were unable to survive in the absence of glucose (Fig. 3). By contrast, cultured human fibroblasts were still viable after 20 hours in the absence of glucose.

These results are consistent with the hypothesis that pituitary adenoma cells are particularly sensitive to glucose deprivation. Whether this sensitivity results from unusu-

FIG. 3. Sensitivity of pituitary adenoma cells to glucose deprivation. **Upper:** Pituitary tumor cells from a patient with Cushing's disease were isolated and exposed to increasing concentrations of glucose in the culture medium. (The normal blood glucose concentration is 1 mg/ml [100 mg/dl].) The tumor cells do not survive with acute deprivation of glucose. Viability was measured by a colorimetric cell proliferation assay (Aqueous One Proliferation Assay Solution [Promega]). Values are expressed as mean $\pm$ SD ($n = 5$ wells/condition). **Lower:** Two additional pituitary tumors were cultured (1 growth hormone–secreting tumor [left, $n = 4$ wells/condition] and 1 nonsecreting tumor [right, $n = 6$ wells/condition]) in the presence (black bar, 100 mg/dl) or absence (gray bar) of glucose. Normal human fibroblasts (ATCC) were included as a nontumor control cell type ($n = 5$ or 6 wells/condition). Pituitary tumor cells (Pit) were sensitive to the absence of glucose, whereas the fibroblasts (Fib) were not.

ally high energy demand or from an inability to use alternative energy sources, or some combination of these two possibilities, remains to be determined.

Discussion

Patients with the typical clinical presentation of apoplexy of a pituitary adenoma generally have macroadenomas and complain of headache, generalized weakness, loss of vision caused by compression of their optic nerves or chiasm, and diplopia caused by dysfunction of the cranial nerves controlling ocular movement. Further, ischemic infarction can occur and produce symptoms and signs in patients with microadenomas.²⁸ It also occurs silently without production of symptoms, as shown by histological features consistent with apoplexy in as many as 25% of microadenomas removed surgically.^{24,37}

Previously proposed mechanisms for pituitary apoplexy include reduced blood supply to the tumor produced by events such as hypotension, rapid growth outpacing the development of adequate blood supply to the tumor,¹² direct pressure by the tumor on the portal vessels or the hypophyseal arteries causing acute ischemia of the tumor,³² increased intratumoral pressure which itself acutely impairs the blood flow to the tumor,⁴⁷ increased metabolic activity beyond adequate arterial supply after stimulation with hypothalamic releasing factors,³¹ and hemorrhage resulting from fragility of the tumor vessels.¹⁰

There is evidence supporting these proposed mechanisms as contributing factors in acute pituitary apoplexy. Increased intrasellar pressure has been documented consistently by measurements made at surgery in patients with macroadenomas.^{1,19–21} It has also been established in patients with pituitary apoplexy,⁴⁷ although it cannot be known if the increased pressure was a consequence of the apoplexy or the cause of it. Thus, the consistency of the pressure measurements and the nearly universal production of a histological pseudocapsule by the intratumoral pressure in small and large tumors,²⁷ increased pressure within the tumor that alters perfusion of it, and associated limited vascularity (see above) are baseline circumstances in all of these tumors. Something else seems to be needed to set the stage for infarction, either with the acute clinical event of clinical apoplexy or with clinically silent infarction.

Although the consistent high uptake of glucose and methionine by pituitary adenomas and the reduced angiogenesis, reduced microvascular density, and limited blood flow in pituitary tumors has been known for some time, it is surprising that none of these features have previously been proposed as setting the stage for spontaneous tumor infarction, which occurs more frequently in pituitary tumors than in any other tumor of the central nervous system. We offer that apoplexy of a pituitary adenoma is the product of intrinsic features of these tumors leaving the tumor in a state of tenuous balance between high metabolic demand, which, based on PET imaging, exists with large and small adenomas, and marginal blood supply, which exists in large and small tumors, in relation to that demand. This would make the tumor vulnerable to acute ischemia by any general event that acutely alters

the balance between tumor blood flow and metabolism, such as systemic hypotension, decreased supply of nutrients, such as hypoglycemia with insulin administration, or by increasing the tumor's metabolic demand with administration of hypothalamic releasing factors. Our laboratory examination of the vulnerability of these tumors to diminished glucose indicates their peculiar susceptibility to deprivation of nutrients such as glucose. Although an increase in the imbalance between metabolic demand by the tumor and its blood flow can be precipitated by abrupt events that alter blood supply to the tumor, such as hypotension associated with surgery, or increased metabolic demand by the tumor after administration of hypothalamic releasing factors, by virtue of these intrinsic features of pituitary tumors a baseline imbalance exists even without these precipitating events. In fact, most pituitary apoplexy occurs in the absence of one of the known acute predisposing events, perhaps as a result of spontaneous fluctuations in the metabolic activity or intratumoral pressure and perfusion in individual tumors that are teetering on a precarious balance of high metabolic demand and limited perfusion. Finally, the mechanism proposed also might explain why it is that the tumor is selectively vulnerable to infarction compared with the normal gland.

The mechanism that we propose here offers therapeutic opportunities to induce selective infarction of an adenoma. These include manipulation of perfusion of the tumor with controlled systemic hypotension, controlled hypoglycemia using graded doses of insulin or by using intravenous deoxyglucose to compete with blood glucose, or intravenous administration of selected hypothalamic releasing factors, used alone or in various combinations, to tip the balance in favor of ischemia selective to the tumor. Any of these approaches would need to be studied initially with smaller tumors that were refractory to standard therapies, in order to avoid the known risks of inducing pituitary apoplexy in a larger tumor. The clinical possibilities of this strategy will require appropriate preclinical studies to investigate safety issues as well antitumor potential. In this respect it is noteworthy that many patients with pituitary apoplexy can be managed successfully with conservative, nonsurgical therapy with the same general success with long-term tumor control as occurs in surgical patients.^{3,17,37} It should also be noted that this approach, if successful, would provide the potential of a tumoricidal treatment of these tumors, rather than the tumor-stabilizing effect of current medical therapies.

Conclusions

Pituitary adenomas undergo spontaneous infarction—pituitary apoplexy—more frequently than any other type of tumor of the CNS. Unusual features of their physiology for a benign tumor include unusually high metabolic demand for glucose and amino acids and limited vascularity. These intrinsic features predispose them to apoplexy, with or without obvious precipitating events, and may provide opportunities for the development of new therapies.

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Author Contributions

Conception and design: both authors. Acquisition of data: both authors. Analysis and interpretation of data: both authors. Drafting the article: both authors. Critically revising the article: both authors. Reviewed submitted version of manuscript: both authors. Approved the final version of the manuscript on behalf of both authors: Oldfield. Statistical analysis: Merrill. Administrative/technical/material support: both authors. Study supervision: both authors.

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