Surgical intervention for pituitary apoplexy: an analysis of functional outcomes

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OBJECTIVE Pituitary apoplexy is a clinical syndrome consisting of neurological and endocrine abnormalities secondary to hemorrhage or ischemia of an underlying pituitary adenoma. The authors investigated whether there was a significant difference in neurological, endocrine, and nonneuroendocrine outcomes for patients with pituitary apoplexy, based on the time between symptom onset and surgical intervention.

METHODS The authors retrospectively analyzed the medical records of 32 patients who had presented to their institution with acute pituitary apoplexy and subsequently undergone endonasal transsphenoidal resection in the period from 2003 to 2014. All patients had undergone preoperative MRI demonstrating evidence of apoplexy in the form of intratumoral hemorrhage, ischemia, and necrosis. Neurological deficits, partial or complete endocrinopathy, and nonneuroendocrine abnormalities were analyzed both pre- and postoperatively.

RESULTS Preoperatively, neurological deficits including visual loss and cranial nerve palsies were found in 31 (97%) of the 32 patients, endocrinopathy in the form of partial or panhypopituitarism was seen in 28 patients (88%), and nonneuroendocrine signs and symptoms were seen in 32 patients (100%). Thirteen patients (41%) underwent surgery within 72 hours of symptom onset ("early"), whereas 19 patients (59%) underwent surgery more than 72 hours from symptom onset ("delayed"). Early versus delayed resection did not appear to significantly improve visual deficits, total visual loss, resolution of oculomotor palsy, recovery from hypopituitarism, or nonneuroendocrine signs and symptoms such as headache and encephalopathy. Overall, visual improvement was seen in 77% of patients, complete restoration of normal vision in 38% of patients, and resolution of preoperative oculomotor palsies in 81% of patients. Only 6 (21%) of 28 patients showed evidence of partial hormone recovery following preoperative hypopituitarism. An absence of benefit for early surgery held true even when considering time to surgery from symptom onset as a continuous variable.

CONCLUSIONS Neurological deficits such as visual loss and cranial neuropathies show moderate improvement following surgical decompression, as does preoperative hypopituitarism. The timing of surgical intervention relative to the onset of symptoms does not appear to significantly affect the resolution of neurological or endocrinological deficits.

<https://thejns.org/doi/abs/10.3171/2017.2.JNS1784>

KEY WORDS apoplexy; deficit; endocrine; neurological; pituitary surgery; visual

PITUITARY apoplexy is a clinical syndrome consisting of neurological deficits and endocrine abnormalities secondary to hemorrhage and/or ischemia of an underlying pituitary adenoma, resulting in tumor necrosis, edema, and expansion.^{22,25,26,36} Neurological deficits may be directly attributable to increased intrasellar pressure from adenoma expansion with resultant mass effect on adjacent cranial nerves (CNs). The loss of visual acuity and visual field deficits are caused by suprasellar expansion with pressure on the optic nerves or chiasm, while

diplopia, ptosis, and partial or complete ophthalmoplegia can result from mass effect on CNs III, IV, and VI.¹¹ Endocrinopathy in the form of partial or panhypopituitarism is also commonly encountered, likely from critical glandular compression following intratumoral hemorrhage or from necrosis of intrasellar contents following ischemia. Additionally, patients can present with severe headache, nausea, vomiting, lethargy, obtundation, and even nuchal rigidity mimicking subarachnoid hemorrhage.

With an incidence ranging from 2% to 20% among pa-

ABBREVIATIONS CN = cranial nerve; GTR = gross-total resection; STR = subtotal resection.

SUBMITTED January 9, 2017. **ACCEPTED** February 24, 2017.

INCLUDE WHEN CITING Published online September 15, 2017; DOI: 10.3171/2017.2.JNS1784.

tients presenting with pituitary adenoma,¹³ apoplexy has classically been considered an acute medical and surgical emergency. In its most extreme form, pituitary apoplexy can be life-threatening due to acute hypocortisolemia from the sudden loss of adrenocorticotrophic hormone (ACTH) production, acute or chronic hypothyroidism, and severe hyponatremia or diabetes insipidus. Reversal of acute vision loss or ophthalmoplegia is also a commonly cited reason for emergent resection and decompression of apoplectic tumors. Nevertheless, there remains an unclear association between time to surgical intervention and rates of neurological and endocrine recovery. The relatively limited case series in the literature have also made it difficult to ascertain predisposing factors for pituitary apoplexy, although larger tumor size, anticoagulation, patient age, hypertension, pregnancy, and diabetes mellitus have been implicated.^{23,26,32,34} Further complicating analyses of pituitary apoplexy, some studies have divided patients into those with acute versus subacute apoplexy. Acute apoplexy—the development of sudden symptoms with evidence of mass effect from an associated hemorrhagic or infarcted adenoma—has been distinguished from subclinical apoplexy^{9,25,37}—a minimally symptomatic or asymptomatic patient with evidence of an infarcted or hemorrhagic tumor—but the clinical significance of this distinction remains unclear.

Despite efforts to operate in an urgent fashion, there is often a time delay between the onset of symptoms and transsphenoidal surgery for acute pituitary apoplexy, often because of delayed patient presentation to a health care provider or emergency room or because of delays in patient transfers to centers able to provide comprehensive surgical and medical care for apoplexy. In an effort to determine the correlation between functional outcomes in patients with acute pituitary apoplexy and time from symptomatic onset to surgery, we report our experience in the surgical management of acute pituitary apoplexy.

Methods

Study Design

We performed a retrospective observational study of our series of pituitary apoplexy patients. All patients were enrolled and consented to research participation under approval of our university's institutional review board, known as the Committee on Human Research.

Patient Cohort

We retrospectively reviewed the records of all patients who had undergone treatment of pituitary adenoma in the period from 2003 to 2014, identifying 32 patients who had presented with acute pituitary apoplexy, all of whom underwent endonasal transsphenoidal resection of a pathologically confirmed necrotic and/or hemorrhagic pituitary adenoma. Patients were followed up until 2014, and data collection and analysis were performed in 2016.

All patients had undergone preoperative MRI or CT demonstrating evidence of apoplexy in the form of intratumoral hemorrhage, ischemia, and necrosis. Patient records were further reviewed to collect demographic data including age, sex, timing of symptom onset, neurological defi-

cits, endocrinopathies, nonneuroendocrine symptoms, hyponatremia, treatment course, postoperative hormone replacement, and follow-up duration. Only patients with the onset of clinical symptoms secondary to mass effect from apoplectic adenomas were included in our case series.

Tumor Characteristics

Data on tumor characteristics such as size, functionality (hormonally hypersecreting versus nonfunctional), pathological staining, invasion, extent of resection, and recurrence rates were collected and analyzed. Functionality was determined on the basis of histological staining in conjunction with laboratory evidence of an abnormal preoperative hormonal elevation. Cavernous sinus invasion was assessed using the Knosp criteria,¹⁴ with Grades 3 and 4 (tumor invasion beyond a line tangential to the lateral margins of the cavernous internal carotid artery, and total internal carotid artery encasement, respectively) designating positive cavernous sinus invasion. Suprasellar invasion was defined as tumor displacement or abutment of the optic chiasm. Recurrence was determined radiologically, defined as either MRI evidence of tumor reappearance following primary gross-total resection (GTR) or as MRI evidence of tumor progression of known residual disease following primary subtotal resection (STR). Time until recurrence was defined as the time from primary resection until the most recent MRI study showing absent disease, stable residual disease, or recurrent disease.

Symptom Classification and Outcome

Signs and symptoms attributable to pituitary apoplexy were subdivided into 3 groups: 1) neurological, 2) endocrine, and 3) nonneuroendocrine. Recorded neurological signs and symptoms included those referable to local mass effect from apoplectic tumors including dysfunction of CN II (blurry vision, field cuts, blindness), CN III (diplopia, ptosis, mydriasis, ophthalmoplegia), CN IV (diplopia, ophthalmoplegia), and CN VI (diplopia, ophthalmoplegia). Postoperative neurological outcomes were further analyzed by recovery of 1) CN II function (visual changes) and 2) CN III, IV, and VI function (cranial neuropathies). Endocrine signs and symptoms were assessed using pre- and postoperative laboratory testing to determine rates of hypopituitarism, hyponatremia, diabetes insipidus, adenoma functionality, and the need for partial or complete postoperative hormone replacement. Nonneuroendocrine signs and symptoms were recorded and included preoperative rates of headache, nuchal rigidity, nausea and/or vomiting, and encephalopathy (altered mental status).

Early Versus Delayed Surgical Intervention

“Early” surgical intervention was defined as resection performed within 72 hours of symptom onset, whereas “delayed” surgical intervention was defined as resection beyond 72 hours of symptom onset. Given that only 2 patients in our cohort underwent resection within 24 hours of symptom onset, the 72-hour time point was chosen to stratify patients into reasonably sized cohorts undergoing surgery in an early versus delayed manner relative to symptom onset. Improvements in neurological and endo-

crine signs and symptoms were each analyzed by early versus delayed surgical intervention.

Statistical Analysis

All statistical analysis was performed using SPSS Statistics Developer 23.0 (IBM Corp.) with significance defined as $p < 0.05$. Chi-square and Fisher's exact tests were used for categorical variables, the Student t-test for continuous variables, and the log-rank test for recurrence data.

Results

Patient Cohort and Presentation

From 2003 to 2014, 32 patients presented with acute pituitary apoplexy. There were 21 males (66%) and 11 females (34%), ranging in age from 10 to 79 years old (mean age 49 years).

Neurological deficits were found in 31 (97%) of 32 patients preoperatively: 25 patients (78%) suffered blurry vision, 15 patients (47%) suffered field cuts and/or subjective visual loss, and 16 patients (50%) suffered from CN III, IV, and/or VI neuropathy (Table 1). Of those patients with vision loss, 6 (40%) suffered acute vision loss within 24 hours of symptom onset, including 1 case of monocular blindness and 5 cases of binocular field cuts and/or blindness; 9 patients (60%) suffered progressive vision loss over days to weeks consisting of blurriness and/or worsening visual acuity, including 3 cases of binocular blindness, 2 cases of monocular blindness, 1 case of a monocular field cut, 1 case of bitemporal hemianopia, and 2 cases of worsened binocular visual acuity.

Endocrinopathy in the form of partial or panhypopituitarism was seen in 28 patients (88%) preoperatively (Table 1). More specifically, hypothyroidism was seen in 13 (43%) of the 30 patients with available preoperative thyroid levels, and hypocortisolemia was noted in 15 (71%) of the 21 patients with available preoperative cortisol levels. Hyponatremia was found in 15 patients (47%) on presentation, including 9 patients with serum sodium values measuring 130–134 mmol/L and 6 patients with values measuring < 130 mmol/L. One patient (3%) presented with diabetes insipidus.

Nonneuroendocrine signs and symptoms were also common (Table 1), seen in all 32 patients (100%). Headache occurred in 32 patients (100%), nausea and vomiting in 10 patients (31%), encephalopathy in 6 patients (19%), and nuchal rigidity in 4 patients (12%). Twenty-three patients (72%) suffered the acute onset of headaches, while the other 9 patients (28%) presented with subacute headaches that progressively worsened. Two patients (6%) were intoxicated on methamphetamine on presentation. Initially, 5 patients had workups for subarachnoid hemorrhage prior to the diagnosis of apoplexy, 4 of whom (80%) showed evidence of increased cerebrospinal fluid leukocytes, erythrocytes, and protein on lumbar puncture.

Neuroimaging Features

As assessed on preoperative MRI, 22 (73%) of 30 patients showed evidence of intratumoral intrinsic T1 hyperintensity indicative of hemorrhage and blood products. The presence of intratumoral hemorrhage was not associ-

TABLE 1. Rates of pre- and postoperative deficits among apoplexy patients

Signs & Symptoms	Preop	Postop
Neurological	97%	
Vision loss or blurriness	97%	23%
CN III, IV, &/or VI neuropathy	50%	24%
Endocrinopathy	88%	69%*
Hyponatremia	47%	NA
Non-NE	100%	
Headache	100%	19%
Nausea/vomiting	31%	0%
Encephalopathy	19%	0%
Nuchal rigidity	12%	0%

NA = data not available; NE = neuroendocrine.

* As determined among 18 patients with available hormone follow-up performed at least 6 months postoperatively.

ated with preoperative visual loss ($p = 1.0$, Fisher's exact test), preoperative CN III, IV, or VI neuropathy ($p = 0.689$, Fisher's exact test), preoperative hypopituitarism ($p = 1.0$, Fisher's exact test), or time (days) from symptom onset to surgery ($p = 0.548$, t-test).

Furthermore, the presence of hemorrhage did not have an effect on visual improvement ($p = 1.0$, Fisher's exact test), total visual recovery ($p = 1.0$, Fisher's exact test), improved oculomotor palsies ($p = 1.0$, Fisher's exact test), endocrine recovery ($p = 1.0$, Fisher's exact test), and non-neuroendocrine symptoms ($p = 0.647$, Fisher's exact test) including postoperative headaches ($p = 1.0$, Fisher's exact test).

Seventy-one percent of patients showed evidence of sphenoid sinus mucosal inflammation, thickening, and contrast enhancement, features that have been previously associated with apoplectic tumors.¹⁶

Baseline Demographics and Rates of Early Versus Delayed Treatment

All patients underwent endonasal transsphenoidal resection of their apoplectic pituitary adenomas. Early surgery, defined as resection within 72 hours of symptom onset, occurred in 13 patients (41%), whereas delayed surgery, defined as resection more than 72 hours from symptom onset, occurred in 19 patients (59%), including 3 (9%) in whom surgery was performed at 2–3 weeks from the time of symptom onset (Table 2). When comparing baseline characteristics between early versus delayed surgery cohorts, there were no significant differences in patient sex ($p = 0.283$, Fisher's exact test) or age ($p = 0.328$, t-test).

Pathology

Five tumor samples (16%) sent for pathology lacked enough viable tumor to establish biochemical diagnosis. Among the 27 successfully tested tumor samples with viable tissue, there were 19 nonfunctional adenomas (70%), 4 lactotrophs (15%), 1 somatotroph (4%), 2 corticotrophs (7%), and 1 mixed lactotroph/somatotroph (4%; Table 3). Four patients (15%) had clinically hypersecreting adeno-

TABLE 2. Comparison of baseline characteristics between early and delayed treatment groups as defined by resection earlier or later than 72 hours from the time of symptom onset, respectively

Parameter	Early Surgery	Delayed Surgery	p Value
No. of patients	13 (41%)	19 (59%)	
Sex	6F/7M	5F/14M	0.283
Mean age in yrs	45	51	0.328
Mean tumor size in cm	3.1	2.8	0.177
Tumor functionality	8%	16%	0.629
Cavernous sinus invasion	17%	40%	0.128
Suprasellar invasion	100%	95%	1.0
Patients w/ GTR*	100%	44%	0.003
Preop hypopituitarism	69%	100%	0.02

Boldface type indicates statistical significance.

* Based on available postoperative scans in 27 of the 32 patients: 11 of 11 patients who underwent early surgery and 7 of 16 patients who underwent delayed surgery.

mas including 3 prolactinomas (11%) and 1 somatotrophinoma (4%). Two patients (6%) were diagnosed with atypical tumors on final pathology, and both were found to be prolactinomas. One patient with a known nonatypical prolactinoma had been medically managed with cabergoline but nonetheless progressed to apoplexy.

Extent of Resection for Early Versus Delayed Treatment

Postoperative scans were available in 27 of 32 patients, confirming 18 GTRs (67%) and 9 STRs (33%). There was a significant difference in the extent of resection in the early versus delayed surgery subgroups (Table 2). Gross-total resection was achieved in 11 (100%) of 11 patients undergoing early surgery versus 7 (44%) of 16 patients undergoing delayed surgery ($p = 0.003$, Fisher's exact test), despite the absence of significant baseline differences between the early and delayed groups in terms of tumor size ($p = 0.177$, t -test), cavernous sinus invasion ($p = 0.128$, Fisher's exact test), or suprasellar invasion ($p = 1.0$, Fisher's exact test). Intratumoral hemorrhage on presentation had no effect on rates of resection ($p = 0.382$, Fisher's exact test).

Visual Outcomes for Early Versus Delayed Treatment

Among patients undergoing early versus delayed resection, there was no significant difference in the baseline rate of preoperative visual dysfunction (92% vs 100%, respectively, $p = 0.406$, Fisher's exact test) including more specifically visual loss and field cuts (69% vs 32%, respectively, $p = 0.070$, Fisher's exact test). Early resection did not appear to significantly improve visual signs and symptoms as compared with delayed resection: visual improvement was seen in 8 (67%) of 12 patients undergoing early surgery versus 16 (84%) of 19 patients undergoing delayed surgery ($p = 0.384$, Fisher's exact test; Table 4). Complete resolution of preoperative decreased visual acuity or field cuts was seen in 4 (33%) of 12 patients undergoing early surgery versus 7 (41%) of 17 undergoing delayed surgery ($p = 0.717$, Fisher's exact test). Overall, 38% of patients with preoperative decreased visual acuity or field cuts

TABLE 3. Baseline characteristics among 27 patient with apoplectic adenomas*

Variable	Value
Mean tumor size in cm (range)	2.9 (1.8–4.1)
Macroadenoma	100%
Cavernous sinus invasion	34%
Suprasellar invasion	97%
Nonfunctional adenoma	70%
Clinically hypersecreting adenoma	15%
Prolactinoma	11%
Somatotrophinoma	4%
Hormone+ pathology	30%
Prolactin+	15%
Growth hormone+	4%
ACTH+	7%
Prolactin+/growth hormone+	4%

ACTH = adrenocorticotrophic hormone; + = positive.

* Twenty-seven patients had enough viable tumor to establish a biochemical diagnosis.

achieved complete restoration of their vision, regardless of time from symptom onset to surgery.

There were no significant differences in the baseline rates of preoperative CN III, IV, and VI neuropathies ($p = 1.0$, Fisher's exact test) between the patient cohorts. Neither was early resection associated with improvement in CN palsies as compared with delayed resection: 5 (83%) of 6 early surgery patients with preoperative palsies showed CN improvement versus 8 (80%) of 10 delayed surgery patients ($p = 1.0$, Fisher's exact test; Table 4).

Endocrine Outcomes for Early Versus Delayed Treatment

There was a significant difference in the rate of preoperative hypopituitarism between the early and delayed treatment patients (Table 2). While 9 (69%) of 13 patients undergoing early surgery suffered preoperative hypopituitarism, all 19 patients (100%) undergoing delayed surgery suffered preoperative hypopituitarism ($p = 0.02$, Fisher's exact test). Nevertheless, among patients with preoperative hypopituitarism, there was no significant difference in the rate of hormone recovery between those undergoing early versus delayed surgery (30% vs 20%, $p = 0.653$, Fisher's exact test; Table 4) or in the time until hormone recovery (80 vs 72 months, $p = 0.784$, log-rank). Recovery tended to happen relatively early posttreatment: 5 of 6 patients recovered function within 7 months, whereas 1 patient showed evidence of recovery at 16 months. Endocrine follow-up ranged from 1 to 121 months postoperatively, with an average of 7 years.

Outcomes for Nonvisual and Nonendocrine Symptoms for Early Versus Delayed Treatment

There were no significant differences in preoperative nonneuroendocrine symptoms, including headache ($p = 1.0$, Fisher's exact test), encephalopathy ($p = 0.194$, Fisher's exact test), nuchal rigidity ($p = 1.0$, Fisher's exact test), or

TABLE 4. Comparison of neurological, endocrine, and nonneuroendocrine deficits between early and delayed surgery groups

Outcome	Early Surgery	Delayed Surgery	p Value
Neurological deficit			
Improved vision	67%	84%	0.384
Total resolution of visual deficits	33%	41%	0.717
Improved cranial neuropathies	83%	80%	1.0
Endocrinopathy			
Improved hypopituitarism	30%	20%	0.653
Non-NE signs & symptoms			
Improved headache	85%	79%	1.0
Improved encephalopathy	100%	100%	—
Improved nuchal rigidity	100%	100%	—
Improved nausea/vomiting	100%	100%	—

— = not applicable.

nausea and vomiting ($p = 1.0$, Fisher's exact test) between the early and delayed treatment patients. These symptoms tended to improve after surgery (Table 4), and patients undergoing early surgery were no more likely than those undergoing delayed surgery to show improvement in these nonneuroendocrine signs and symptoms: 10 (77%) of 13 patients in the early treatment group showed improvement versus 15 (83%) of 18 patients in the delayed treatment group ($p = 0.676$, Fisher's exact test).

Outcomes Based on Varied Time to Surgery From Symptom Onset and Time of Admission

Overall, 2 patients (6%) underwent surgery within 24 hours of symptom onset, 5 (16%) at 48 hours from symptom onset, and 6 (19%) at 72 hours from symptom onset. Additional analysis revealed that separating patients based on a 48-hour time point rather than a 72-hour time point was no more likely to show recovery of neurological, endocrine, or nonneuroendocrine function than those treated beyond 48 hours.

When considering time to surgery from symptom onset as a continuous variable, there was no significant association between improved neurological, endocrine, or nonneuroendocrine function and time until surgery. This also held true when considering time to surgery from hospital admission: there was no association between time to the operating room from admission and improved neurological, endocrine, or nonneuroendocrine function.

Discussion

Given the complex presentations and outcomes associated with pituitary apoplexy, we sought to better analyze the importance of surgical timing in the treatment of acute pituitary apoplexy. We focused solely on surgical treatment rather than medical therapy, as our patient cohort overwhelmingly presented with evidence of visual deficits and/or cranial neuropathies and all underwent resection as a result.

In contrast to “subacute” or “subclinical” apoplexy in which radiographic evidence of tumor hemorrhage or infarction is seen with atypical or absent clinical symptoms, “acute” apoplexy was the exclusive focus of our series. Two recent studies comparing subclinical and classic apoplexy determined that subclinical cases occur more frequently than the classic and show comparable visual and endocrine recovery,^{17,37} but we believe that subclinical cases represent a different pathological process and did not include similar cases in our cohort.

Our male preponderance of patients reflects a slight gender gap seen in other larger studies of apoplexy,^{4,18,26} in which men appear to outnumber women by 2:1. Similarly, our mean age of 49 years reflects the more common distribution of patients in their 5th and 6th decades of life at presentation.³⁰ All tumors in our case series were macroadenomas, and as occurs in the published literature,^{3,4,18,23,26,27} our case series comprised mostly nonfunctional adenomas (70%), with only 15% of adenomas demonstrating hormone hypersecretion (3 prolactinomas, 1 somatotrophinoma). The fact that apoplexy is more often associated with larger tumors, which is well reported in the literature,^{6,7,18,20,23,30,33,36} is purportedly due to the increased tumor size outstripping blood supply and resulting in ischemia and/or hemorrhage. It has been suggested that features intrinsic to the biology of apoplectic adenomas, such as high metabolic demand with concomitant limited vascular supply, hypoglycemia, and limited nutrient supply, may predispose to ischemia and hemorrhage.²⁴

Despite an increasingly nuanced view of treatment for acute pituitary apoplexy in which the literature has revealed an expanding role for nonsurgical conservative therapy in select cases—most often those cases without visual compromise^{3,5,10,19,29,30}—optimal timing for treatment remains unclear. This combined with anecdotal evidence that apoplectic tumors may regress following conservative management^{12,38} makes it increasingly evident that acute pituitary apoplexy is not a uniform diagnosis or disease entity. Our longstanding practice has been emergent resection for acute pituitary apoplexy following preoperative endocrinological and medical stabilization, for example, normalization of hypocortisolism, hypothyroidism, and hyponatremia. This practice most likely reflects the high rate of visual compromise in our cohort; we report that 31 (97%) of 32 patients possessed some form of visual compromise in the form of visual loss and/or CN III, IV, and/or VI neuropathies, which prompted our group to perform endonasal transsphenoidal resection to remove tumor and relieve mass effect. Thus, while our study is not equipped for an analysis of medical versus surgical outcome, our similar rates of baseline neurological and nonneurological deficits allowed us to perform a head-to-head comparison among patients undergoing early versus delayed surgical treatment. Delays in time to treatment were attributable to delayed patient presentation to medical attention or to transfer delays from referring institutions.

The only differences in baseline characteristics between our 2 patient cohorts were the higher prevalence of hypopituitarism seen in the delayed treatment cohort and higher rates of GTR in the early treatment group. We interpret the former finding as most likely reflective of the

delayed manner in which ischemia and infarction of an apoplectic adenoma cause glandular compromise and necrosis, whereas the latter finding suggests that the loss of tumor architecture, pseudocapsule, and glandular interface in apoplectic tumors may make it more difficult to achieve GTR. Our analysis of hemorrhagic tumors and extent of resection showed no association between hemorrhage and resectability, raising the possibility that a tumor's gross consistency may not be the only factor predicting resectability and that features intrinsic to apoplectic tumors may render them more difficult to resect following an initial apoplectic infarction or hemorrhage.

While statistically insignificant, the trend toward greater visual loss and field cuts at presentation for patients who underwent early rather than delayed surgery is nevertheless an important caveat for our study. It raises the possibility that early treatment of more severe symptomatology may be necessary to ensure outcomes similar to patients undergoing delayed treatment of more moderate symptomatology and that our patient numbers were simply underpowered to detect a bias toward treating certain apoplexy patients earlier. Indeed, the literature frequently glosses over the use of surgical intervention for "more severe" cases versus conservative medical therapy for patients without acute vision loss or ophthalmoplegia, but this bias toward treating apoplectic patients differently based on acuity of presentation makes it impossible to draw firm conclusions about ideal treatment. We have shown a statistically insignificant ($p = 0.07$) difference in baseline rates of visual deficits between our 2 treatment groups, allowing us to more accurately determine the lack of an association between treatment timing and outcome, though more robust patient numbers collected in a prospective fashion would undoubtedly bolster our argument and strengthen our statistics.

A litany of retrospective studies^{1,3–5,10,15,18,19,26,29} have attempted to stratify patients by optimal medical versus surgical management but have yielded largely conflicting results; a recent meta-analysis suggested an improvement in visual and endocrine outcomes in patients undergoing resection³¹ but reviewed too few studies to claim statistical significance and included only retrospective studies. Few papers directly address the matter of optimal timing of surgical intervention independent of comparisons to medical therapy, and those that do have also yielded conflicting results.

In a 2016 study of 31 patients with classic pituitary apoplexy, Giritharan and colleagues⁸ treated 11 patients conservatively, 11 with emergent surgery within 7 days of presentation, and 9 with surgery more than 7 days from presentation. The authors did not find any statistically significant differences in the rates of visual or endocrine recovery among the groups, despite the fact that the emergent surgery cohort possessed higher rates of baseline visual and endocrine dysfunction. Bujawansa and colleagues⁵ similarly concluded that there was no clear visual, CN, or endocrine benefit to early surgical (< 7 days) versus late surgical (> 7 days) intervention, either in a head-to-head comparison or when compared with medical management, with the major caveat that Pituitary Apoplexy Scores were significantly higher in the early surgery group. Singh et al.³⁰ performed a similar study on medical versus early and

delayed surgery for acute apoplexy, concluding that medical therapy was a viable treatment option given the lack of clear benefit seen among the surgical cohorts. Their study did not use a fixed cutoff for early versus delayed surgery, however, and patients undergoing early surgery tended to have more severe visual deficits at presentation.

In contrast, Bills et al.⁴ published the results of their surgical management of apoplexy prior to 1992 and affirmed a role for early surgery, defined as < 7 days, with statistically significant improvements seen among patients with visual deficits. Interestingly, a subgroup analysis of patients who underwent surgery within 3 days of presentation versus 4–7 days did not show a difference in visual outcomes, similar to findings in our study. Randeva and colleagues²⁶ similarly concluded that patients undergoing resection within 8 days of symptom onset demonstrated significantly superior visual outcomes compared with those undergoing delayed surgery, though their study did not find a difference in rates of ocular paresis improvement. Seuk et al.²⁸ showed a statistically significant improvement in visual acuity and field cuts among patients undergoing resection within 48 hours of symptom onset, while Woo et al. showed a similar improvement in visual deficits with early surgery (< 3 days) versus delayed surgery.³⁵

Endocrine recovery appears to be poor regardless of timing of intervention, consistent with our own findings. While one study² demonstrated improved endocrinological outcomes following early surgery, the case series involved only 8 patients, and numerous other groups have reported uniformly poor endocrine outcomes.^{5,8,10,18,29,30} We found no difference in the rates of hormone recovery between the early and delayed groups. Importantly, we only included patients who had undergone postoperative endocrine testing at least 6 months postoperatively to allow enough time for possible reestablishment of the hypothalamic-pituitary axis. The limited number of patients demonstrating endocrine recovery likely represents those with a stunned but intact pituitary gland. Patients should be counseled that the overall likelihood of the return of function is low and that delayed recovery is unusual.

Nonneuroendocrine symptoms improved regardless of the timing of treatment. Many of the symptoms, such as headache and nuchal rigidity, can be caused by mass effect and are likely to improve with time, regardless of the onset of intervention, whereas systemic features such as nausea/vomiting and encephalopathy can be exacerbated by underlying endocrinopathy and thus are best treated medically.

Importantly, when resection is performed by experienced pituitary surgeons, patients can be counseled that neurological outcomes following surgery remain favorable for acute pituitary apoplexy, despite poor outcomes for the reversal of endocrinopathy. Given the breadth of patient age, presentation, tumor size, hormonal functionality, and variable time from presentation until surgery, we feel our results are externally valid and can apply to other patients who present with pituitary apoplexy.

Our findings suggest that delays in clinical presentation do not adversely impact outcomes in apoplexy patients. Our findings also suggest that time can be taken to pre-

operatively correct endocrinopathies, obtain high-quality imaging for surgical planning, and allow patients to come under the care of experienced pituitary surgeons at dedicated pituitary centers of excellence²¹ without adversely affecting apoplexy patient outcomes. Nevertheless, we still advocate transsphenoidal surgery without excessive delay for apoplexy patients who present with visual deficits given the clear benefits to surgery, regardless of timing.

Study Limitations

As a retrospective case series, our study is inherently limited by selection bias and incomplete documentation or follow-up for all patients. The patients lost to follow-up limit our ability to perform more meaningful neurological and endocrinological postoperative analyses. Where possible, we attempted to limit bias by capturing all apoplexy patients regardless of outcome and to maximize follow-up intervals. While our analyses showed that defining early versus delayed surgery at 48 hours or 72 hours from symptom onset to resection resulted in similar neurological, endocrine, and nonneuroendocrine outcomes, our final selection of 72 hours was chosen to maximize statistical power. A greater number of patients in the earlier treatment groups (24 hours, 48 hours) would facilitate more meaningful statistical analysis.

Conclusions

Acute pituitary apoplexy presents with derangements of neurological and endocrinological function. Neurological deficits such as visual loss and cranial neuropathies show improvement following surgical decompression, with rarer recovery from hypopituitarism, and most patients require long-term hormone replacement. The timing of surgical intervention relative to the onset of symptoms does not appear to significantly affect the resolution of neurological or endocrinological deficits.

Acknowledgments

Dr. Rutkowski received a Precision Health Science TL1 (PRE-SCIENT) Postdoctoral Fellowship training grant.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Rutkowski. Acquisition of data: Rutkowski. Analysis and interpretation of data: all authors. Drafting the article: Rutkowski. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Rutkowski. Statistical analysis: Rutkowski. Study supervision: Kunwar, Blevins, Aghi.

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