



Is it Necessary to Operate on Patients with Pituitary Hemorrhage?

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Abstract

Background: Pituitary tumors are a common pathology in neuro-oncology. It is not uncommon that pituitary apoplexy is the first manifestation of the disease, and the choice of optimal tactic is important. Considering the presence of observations of spontaneous resorption of tumors after pituitary apoplexy, the standard approaches to this pathology require revision.

Objectives: We aim to identifying factors that contribute to tumor resorption and compare conservative and surgical treatment methods.

Methods: We review the results of treatment of 82 patients with pituitary apoplexy. 45 patients were surgically managed and 37 patients were managed conservatively.

Results: Tumor size has a direct link with the rate of spontaneous resorption rates, along with hemorrhage type and localization. Dexamethasone plays an important role in conservative therapy, significantly improving outcome. Conservative treatment methods, when applied with the described algorithm allow for highly efficient results, comparable to urgent surgical intervention.

Conclusion: Based on our results, we propose an updated algorithm for the treatment of patients with pituitary apoplexy. The application of the proposed algorithm will allow in some cases to avoid emergency surgery and obtain a comparable clinical result with lower patient risk.

Keywords: Pituitary apoplexy; Transnasal adenectomy; Pituitary hemorrhage

Introduction

As is known, hemorrhage into the pituitary macroadenoma is an urgent neurosurgical situation due to a sharp increase in the volume of the tumor and compression of surrounding structures, primarily the optic nerves. The main reason for this condition is a presence of a pituitary tumor, which are not uncommon (up to 14% presence in post-mortem autopsies and up to 22.5% in screening X-ray studies) [1-3]. In 80% of cases, such hemorrhaging becomes the first manifestation of the underlying disease, and the risk of its occurrence for each tumor carrier increases by 10% for every 2.5 to 5 years of observation [4-6]. Traditionally, pituitary apoplexy is considered an urgent surgical condition [4,7], at the same time, the rate of spontaneous resorption remain underestimated especially with regard to the possibility of maintaining pituitary functions.

Materials and Methods

We present a series of 82 cases of pituitary apoplexy, managed by both surgical intervention and conservatively. The primary surgical team has experience in transnasal endoscopic surgery on over 4,000 pituitary adenomas and performed all the procedures. More detailed diagnostic issues, morphological features and analysis of literature data on pituitary apoplexy are thoroughly discussed in literature and in our previously published works [8,9].

The patients were separated into two groups: Group 1 included 45 patients who received surgical treatment within 1 month after diagnosis, of which 10 (22.2%) were urgent surgical interventions; Group 2 included 37 patients who were managed conservatively.

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The study was approved by the Ethical Committee (IEC) of the Burdenko Neurosurgical Center.

Results

No significant differences in gender or age were noted between groups ($p > 0.05$). According to tumor size, the tumors were separated into several groups. Smaller tumors prevailed in Group 2 (Figure 1).

Hormonally inactive tumors were most commonly found (in 85.4% of cases). Prolactinomas were three times less common, and somatotropinomas were almost 10 times less common.

According to the time from onset of clinical symptoms until the diagnosis was made and treatment started, we conditionally divided the material into three groups of early (<24 h), timely (1 day to 1 month) and late (over 1 month) diagnosis (Table 1).

Visual field disorder

Visual disturbances were observed in 54 of 82 (65.9%) patients. In 15 of these cases, only conservative treatment was performed. In 39 cases, patients were surgically managed. Dexamethasone was used in the course of treatment in 6 patients in Group 2 and only in 1 of Group 1. Improvement in vision after surgery was noted in 35.9% of cases (14 out of 39) and in 61.5% (24 out of 39) there was no change. Worsening was observed in 1 of 39 (2.6%) cases. In Group 2, improvement in visual functions was noted in 46.7% of cases (7 out of 15) and remained unchanged in 46.7% (7 out of 15). Deterioration occurred only in 1 observation (6.7%). The use of dexamethasone with conservative treatment provided an improvement in vision in 66.7% (4 out of 6) patients. Conservative treatment without the use of Dexamethasone provided an improvement in only 33.3% (3 out of 9). No statistically significant differences were noted between the two groups ($p < 0.05$).

Oculomotor pathology

Oculomotor disorders were noted in 28 out of 82 (34.1%) observations. In half of the cases, they were detected when the hemorrhage was less than 1 month old. In 19 out of 28 (67.9%) cases of oculomotor disorders, time from onset of symptoms did not exceed 3 months. After 3 months the frequency of their detection was significantly reduced. Surgical removal was not performed in 13 of 28

Table 1: Time-based treatment peculiarities.

| Method of treatment | Time since clinical onset to diagnosis | | |
|-----------------------------|--|---------------------------|--------------|
| | <24 hours | Between 1 day and 1 month | Over 1 month |
| Conservative therapy (n=37) | 4 | 27 | 6 |
| Surgical treatment (n=45) | 4 | 6 | 35 |
| Total (n=82) | 8 | 33 | 41 |
| | 9.8% | 40.2% | 50.0% |

(46.4%) patients. In 5 out of 13 (38.5%) patients with dexamethasone, there was a complete (3) or partial regression (2) of nerve insufficiency.

In the remaining 8 out of 13 (61.5%) patients, conservative treatment without the use of dexamethasone resulted in regression of oculomotor disorders in 5 (62.5%) cases. In 2 cases, the disorder did not regress, and in 1 case there an increase in symptoms was seen. However, these differences were not statistically significant ($p < 0.05$), but show an important aspect of conservative therapy failure.

Among 15 out of 28 (53.6%) surgically treated patients who had oculomotor disorders, 12 (80%) of them had regression of oculomotor disorders by the time of discharge. All patients were operated on within 1 month from symptom onset. In 3 cases, when patients were operated on over 1 month after symptom onset, oculomotor functions did not recover. Dexamethasone was used in the treatment of 2 surgically managed patients, who had complete (1) and partial (1) regression of disorders after surgery.

Secondary symptoms

Intense headaches were noted in 81.6% of cases. Further, they persisted in 70% of patients for up to 1 week. Pronounced vasospasm was seen in 1 case with the appearance of multiple ischemic foci in the subcortical nodes, severe subcortical symptoms in the form of tremor, hyperkinesia and severe dysarthria were noted, and in 1 case the appearance of static and coordinating disorders was also seen. Emotional lability and depression were noted in 2 patients. Fixation amnesia was noted in 1 case. In 5 cases, there was a decrease in the level of wakefulness from stunning to somnolence.

Pituitary insufficiency was noted in 41.5% of cases. In 19 out of these 34 cases (55.9%), the duration of the hemorrhage was less

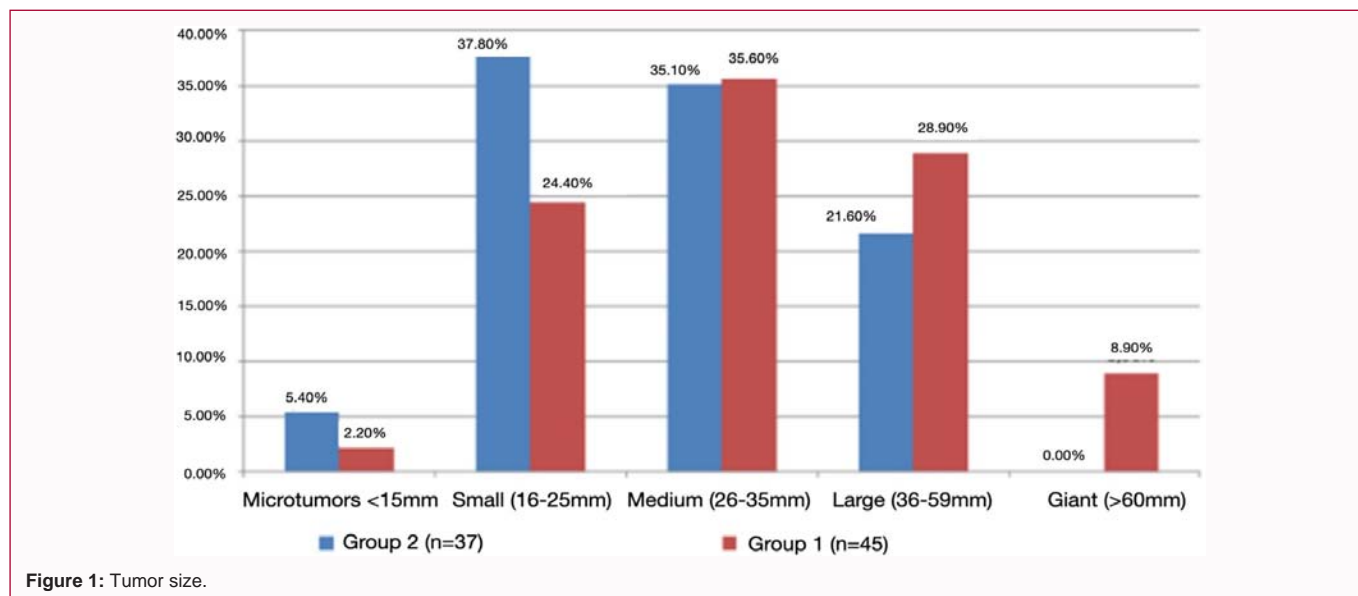


Figure 1: Tumor size.

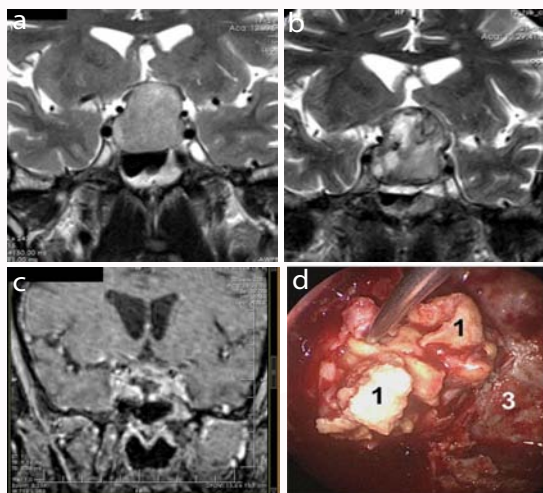


Figure 2: Clinical example of a typical pituitary apoplexy surgically treated one month after hemorrhage (the figure shows intraoperative and diagnostic images of a 56-year-old patient, 1.5 months after the onset of visual impairment: A) MRI reveals a typical pituitary tumor. 2 months after diagnosis, typical clinical manifestations of pituitary apoplexy appeared - acute headache, nausea, vomiting, and a rapid decrease in vision. The patient was hospitalized to the clinic a month after the deterioration of his condition with bilateral amaurosis. B) MRI data showed an increase in the size of the tumor, its stroma became heterogeneous, and edema of the mucous membrane of the sphenoid sinus appeared. C) MRI data 2 months after surgery shows complete tumor removal. In the neurological status after the operation, the appearance of light perception in the right eye was noted, with the preservation of amaurosis on the left. Electric stimulation of the optic nerves did not provide further positive dynamics). D) The tumor was then removed by transnasal access. During surgery, the tumor was seen to be atypical for a pituitary tumor, yellow in color, dense, with difficulty separated from the dura mater.

than 1 month, and over 1 month in 15 (44.1%). It is necessary to separately note the irreversible nature of pituitary disorders that we revealed when dexamethasone was not used in the acute period of hemorrhage. Of 25 patients who did not receive dexamethasone, panhypopituitarism remained on follow-up in 24 (96%). In contrast, regression was noted in 8 of 9 (88.9%) treated with dexamethasone. This difference turned out to be statistically significant ($p < 0.05$).

A significant risk in emergency surgery is the inability to detect and preserve the remnants of the adenohypophysis in the dense imbibed tumor tissue (Figure 2). Of 19 patients with pituitary insufficiency in the first month after the hemorrhage, 7 were surgically treated, and 12 patients avoided surgery. Only 1 out of 7 (14.3%) surgically managed patients showed restoration of pituitary function. In contrast, in patients who received only conservative treatment in the first month after the hemorrhage, the restoration adenohypophysis function occurred in 50% (6 out of 12). However, this difference turned out to be statistically insignificant ($p < 0.05$).

MRI – characteristics of a pituitary hemorrhage. To identify the MRI features of the hemorrhage, we used the data on the most traditionally weighted MRI images - T1 without contrast gain and T2. The results of our analysis are presented in more detail in earlier published work [8]. When evaluating the MRI data, an assessment is made on which part of the tumor volume is within the hemorrhage area and whether the hemorrhage focus is represented by a cyst or diffuse imbibition of the tumor stroma (Table 2).

Morphological evaluation

Morphologically, the removed tumor makes it possible to detect

Table 2: MRI characteristics of pituitary tumor hemorrhage focus at various times from the moment of hemorrhage.

| Time since hemorrhage began | Number of cases | MRI-characteristics | | | |
|-----------------------------|-----------------|---------------------|---------|----------------|---------|
| | | Diffuse imbibition | | Cyst formation | |
| <2 days | 8 | 8 | 100.00% | 0 | 0.00% |
| 2-7 days | 18 | 16 | 88.89% | 2 | 11.11% |
| 7-14 days | 11 | 8 | 72.73% | 3 | 27.27% |
| 14-30 days | 4 | 3 | 75.00% | 1 | 25.00% |
| 1-2 months | 8 | 4 | 50.00% | 4 | 50.00% |
| 2-3 months | 5 | 3 | 60.00% | 2 | 40.00% |
| 3-4 months | 3 | 1 | 33.33% | 2 | 66.67% |
| 4-5 months | 5 | 0 | 0.00% | 5 | 100.00% |
| 5-6 months | 2 | 0 | 0.00% | 2 | 100.00% |
| 6-11 months | 6 | 1 | 16.67% | 5 | 83.33% |
| >12 months | 12 | 0 | 0.00% | 12 | 100.00% |
| Total | 82 | 44 | 53.66% | 38 | 46.34% |

various changes within its stroma: Foci of necrosis, scar tissue, regions unchanged tumor tissue are most common.

Choice of treatment tactic

Our surgical group included 45 patients treated via the transsphenoidal endoscopic approach. 37 patients did not require surgery and were managed conservatively. Choice of treatment depended on indications for urgent surgery: Acute hemorrhage, appearance of neurological deficit (chiasmatic syndrome, oculomotor disorders, cranial pain syndrome), ineffectiveness of conservative therapy. However, not all acute patients were hospitalized in a timely manner and were later managed conservatively, as they no longer fit surgery requirements by admission time due to the phenomenon of spontaneous resorption.

Spontaneous resorption

Spontaneous hemorrhage resorption is one of the most favorable developments in pituitary hemorrhages. Tumor resorption was seen in 89.2% (33 out of 37) of conservative treatment cases. We found that the probability of complete resorption of small tumors (up to 25 mm in size) reached 60%, and for medium and large tumors (26 mm to 59 mm) did not exceed 40%. The size hemorrhage resorption in our series of observations turned out to be less than 40 mm, and we further accept this value as a “threshold” when suggesting an algorithm for choosing an optimal treatment option. Resorption of giant tumors (more than 60 mm) was not seen. The probability of resorption was higher when the focus of hemorrhage was represented by imbibed tumor tissue (63.6%) rather than by a cyst (13.2%). This difference turned out to be statistically significant ($p < 0.001$). We did not observe resorption when the hemorrhage was over 3 months old.

Discussion

Traditionally, pituitary apoplexy is considered as an indication for urgent surgical decompression of the sellar and near-sellar region [4,5,7]. In most cases after surgery an improvement in vision and oculomotor functions is seen. At the same time, pituitary functions are generally not restored. Existing literature describes cases of spontaneous tumor resorption with the possibility of maintaining pituitary functions [10].

The general principles for the diagnosis and treatment of

hemorrhages in a pituitary tumor were summarized by a group of British researchers "Pituitary Apoplexy Guidelines Development Group", as of February 2009 *via* the British Society of Endocrinology. In May 2010, they formulated and later published recommendations for the treatment of hemorrhages in the pituitary tumor - "UK guidelines for the management of pituitary apoplexy" [7]. The algorithm proposed by British colleagues is exclusively "surgical" without taking into account the size of tumors, radiological characteristics of the hemorrhage zone, hormonal activity of the tumor, and even the age of the hemorrhage. The clinical condition of the patient, the severity of symptoms and their dynamics turned out to be decisive in the choice of the treatment method.

Primarily, our results show that treatment effectiveness depends on the severity of the underlying disease and the hemorrhaging complication. Patients treated surgically were mainly subacute and had gradual onset of symptoms, and the hemorrhaging a somewhat anticipated discovery, confirmed by intraoperative visualization and MRI. At the same time, pituitary functions remained intact in the majority of these patients by the time of their hospitalization, despite the fact that dexamethasone was not used in these patients before surgery. In contrast, patients with acute onset, and severe clinical manifestations, required urgent hospitalization, and were treated efficiently as well. A concrete argument in favor of surgical intervention is the possibility of rapid and effective decompression of the optic and oculomotor nerves. At the same time, the likelihood of improvement decreases as the waiting time for surgery increases from the moment of hemorrhage. It is optimal to carry out the operation no later than a month from the moment of hemorrhage.

Unfortunately, when such surgical procedures are performed at such an early stage, it can be very difficult to detect and preserve the remnants of the adenohypophysis in the dense imbibed tumor tissue. Almost none of the urgently operated patients showed recovery of pituitary functions.

Analysis of treatment results in patients who were not surgically managed showed the possibility of recovery with conservative therapy, as well as the possibility of complete tumor resorption. As such, proper management and conservative therapy in some cases provides treatment result comparable and even superior to surgical intervention. The use of dexamethasone significantly improves the results of both surgical and conservative treatment in the acute period.

We therefore suggest conservative treatment to patients with a hemorrhage age of less than 3 months, a maximum tumor size of 40 mm, a hemorrhage focus represented by imbibed tissue (not a cyst), and minimal visual and oculomotor disorders.

Conclusion

The severity of clinical onset, rate of deterioration in the patient's condition, manifestation and range of neurological symptoms and endocrine insufficiency determine the indications for an urgent neurosurgical operation. Nevertheless, in cases where, for a number of reasons, the patient was not operated on in within the first 10 to 14 days from onset of symptoms, it makes sense to clarify the indications for surgery due to the fact that there is a possibility of spontaneous resorption of the hemorrhage, confirmed by the results presented in the article. Conservative treatment, when chosen in accordance to hemorrhage and tumor size, MRI picture, duration of disease and rate of symptom aggravation, provides effective results, while reducing risks of surgical intervention.

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