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# Pituitary apoplexy – an urgent operation or a wait-and-see strategy?

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**Background.** Pituitary tumors are a common pathology in neuro-oncology. They constitute 10 % of all intracranial tumors; and for a long time, they may not have any clinical manifestations. In situations where pituitary apoplexy is the first manifestation of the disease, the choice of optimal tactics is particularly relevant. Considering cases of spontaneous tumor resorption after pituitary apoplexy, the standard approach to this pathology as an exceptional urgent one requires revision.

**Aim.** To review the treatment strategy of patients with pituitary apoplexy, identifying factors contributing to both tumor resorption and achievement of a better clinical result. After specification of the indications for surgery, to create an algorithm for treating patients with pituitary apoplexy.

**Materials and methods.** The paper analyzes the results of treatment of 82 patients with pituitary apoplexy. Only 45 patients were operated on. In 37 patients, the need for surgery ceased during preparation.

**Results.** Analysis of treatment results of 82 patients with pituitary apoplexy identified optimal tumor parameters and radiological characteristics for which the probability of spontaneous resorption is the highest: 89.2 % (33 out of 37) cases. The use of dexamethasone as part of therapy has shown to play a key role in achieving optimal results. The analysis of the data allowed us to formulate criteria for which a wait-and-see tactic in pituitary apoplexy can provide a result comparable to the surgical method of treatment and even surpassing it in terms of preservation of pituitary functions.

**Conclusion.** As a result of the study, an algorithm for treatment of patients with pituitary apoplexy was proposed. The application of the proposed algorithm will allow, in some cases, to forego an emergency surgery and obtain a comparable clinical result with less risk for the patient.

**Keywords:** pituitary adenoma, hemorrhage, endoscopic transnasal surgery

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## BACKGROUND

Hemorrhage into a pituitary tumor (pituitary apoplexy – PA) is a highly relevant problem, as it potentially affects a significant number of people. The prevalence of pituitary tumors, according to current estimates, reaches almost 17 % of the population (ranging from 14 % of autopsy findings to 22.5 % in screening neuroimaging studies) [1–7]. In 80 % of cases, such hemorrhage is the first manifestation of the disease, and the risk of its occurrence for each patient with tumor increases by 10 % for every 2.5–5 years of observation [8–17].

Traditionally, PA is considered as an indication for urgent surgery [8, 9, 18–20], while the results of cases of spontaneous tumor resorption remain underestimated

[21, 22], especially with regard to the possibility of preserving pituitary functions [23–27].

Aim of study – to revise the treatment strategy for patients with PA, identifying factors that contribute to both tumor resorption and achieving the best clinical outcome; to create an algorithm for treating patients with PA by clarifying the indications for surgery.

## MATERIAL AND METHODS

We present the results of our own series of 82 observations, consisting not only of emergency surgical interventions but also of cases in which surgery was avoided. For a team of surgeons with accumulated experience in transnasal endoscopic surgery to remove more than 4,000 pituitary

adenomas, the presented results were simultaneously unexpected and noteworthy [28–31]. Diagnostic issues, morphological features, and analysis of literature data concerning PA are presented in more detail in the literature and in our previously published works [32–45].

The age of hemorrhages ranged from 1 day to over a year. Patients were divided into 2 groups:

- 1) patients who underwent surgical treatment ( $n = 45$ );
- 2) patients without surgical treatment ( $n = 37$ ).

Cases of acute hemorrhages, in which the patient was admitted to the Burdenko National Medical Research Center of Neurosurgery and underwent emergency surgery, were rare: only 10 of 45 (22.2 %) patients were hospitalized and operated on within 1 month of the hemorrhage.

The group of patients who did not require surgery and who received only conservative treatment consisted of those who suffered an acute hemorrhage not in the Burdenko National Medical Research Center of Neurosurgery and were not admitted to our hospital within one month. These patients comprised 31 of 37 (83.8 %). Essentially, this group consisted of patients who, despite initial indications for surgery, no longer required surgical treatment after a course of therapy.

No differences in gender distribution were found in the study group of 82 patients (Table 1). The median age

was 46.5 years. By tumor size, patients were divided according to the classification adopted at the Burdenko National Medical Research Center of Neurosurgery [46]. The small and medium-sized tumors predominated in the group of conservative treatment, while the majority of patient in the “surgical” group had large and giant tumors (Fig. 1). The distribution of the main parameters of the group with PA is described in more detail in our previously published work [42].

The hormonally inactive tumors prevailed in our observation series, accounting for 85.4 %. Prolactinomas were three times less common, and somatotropinomas were almost ten times less common.

By age of hemorrhage, from the onset of clinical symptoms to diagnosis and initiation of treatment, we divided the patients as follows:

- 1) cases of early diagnosis – with sudden clinical onset and deterioration of the patient’s condition over a period of several hours to one day – 8 patients (9.8 %), among them 4 underwent surgery;
- 2) cases of traditional diagnosis – from one day to one month – 33 patients (40.2 %)? Among them only 6 (18.2 %) underwent surgery;
- 3) cases of delayed diagnosis – when it was impossible to accurately determine the date of hemorrhage or

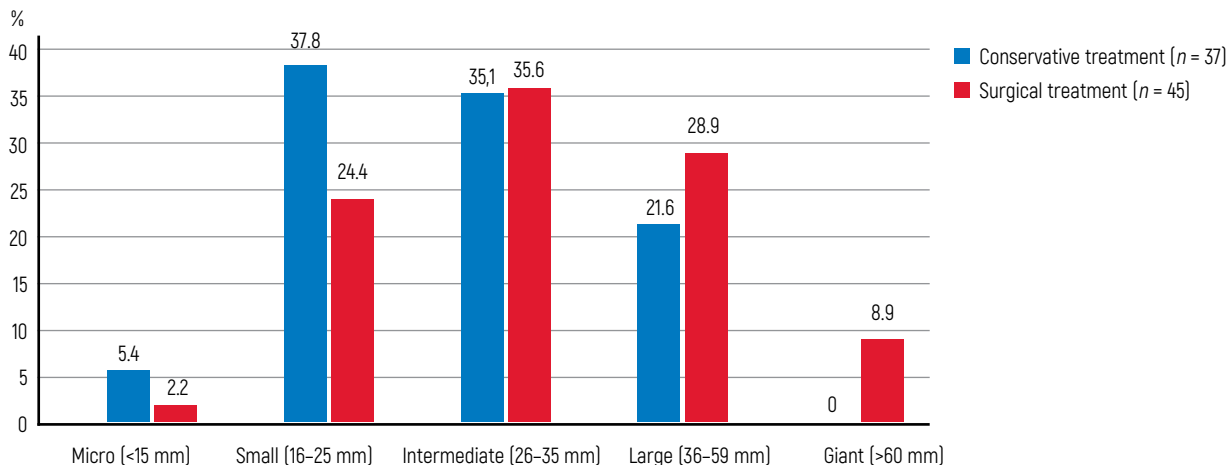


Fig. 1. Distribution of the tumors per size

Table 1. Acuteness of hemorrhage development

Type of treatment	Time since hemorrhage at the time of diagnosis, number of patients		
	Less than 1 day	Between 1 day and 1 month	More than 1 month
Conservative treatment ( $n = 37$ )	4	27	6
Surgical treatment ( $n = 45$ )	4	6	35
Total ( $N = 82$ )	8	33	41
	9.8 %	40.2 %	50.0 %

when the patient's condition gradually worsened over more than one month – 41 patients (50.0 %), among them 35 (85.4 %) underwent surgery.

#### CLINICAL SIGNS OF PITUITARY APOPLEXY AND ITS DYNAMICS DURING TREATMENT

**Visual impairment** was observed in 54 of 82 (65.9 %) patients. Only conservative treatment was performed in 15 cases, and 39 patients underwent surgery. Dexamethasone was used during treatment in six patients in the conservative group and only in one of the patients in surgical group.

Postoperative vision improvement was noted in 35.9 % of cases (14 of 39), and no dynamics were observed in 61.5 % (24 of 39) patients. Deterioration was observed in 1 of 39 cases (2.6 %). Improvement of visual function in group of conservative treatment was noted in 46.7 % of cases (7 of 15) and 46.7 % (7 of 15) patients remained without dynamics. Deterioration occurred in only 1 (6.7 %) case. The use of dexamethasone in conservative treatment ensured vision improvement in 66.7 % of cases (4 of 6 patients). Conservative treatment without the use of dexamethasone ensured improvement in only 33.3 % of cases (3 of 9 patients). These differences were statistically insignificant (Fisher's exact test 0.3).

**Oculomotor disturbances** were observed in 28 of 82 (34.1 %) cases. In half of the cases, these disturbances were detected when the hemorrhage had been present for up to 1 month. In 19 of 28 (67.9 %) cases, the hemorrhage had been present for no more than 3 months. After 3 months, the frequency of these disturbances detection decreased significantly.

Surgery was not performed in 13 of 28 (46.4 %) patients, among them in 5 (38.5 %) patients, complete (3) or partial (2) regression of nerve insufficiency was observed with dexamethasone use. In the remaining 8 of 13 (61.5 %) patients, conservative treatment without dexamethasone resulted in regression of oculomotor disorders in 5 (62.5 %) cases. In remain 2 cases, the insufficiency did not regress, as well as in 1 case, an increase in the insufficiency was observed. However, these differences were not statistically significant, and only a trend can be assessed.

#### RESULTS

Among 15 of 28 (53.6 %) operated patients who had oculomotor impairments before surgery, 12 (80 %) had regression of these disturbances at discharge. All patients were operated on within 1 month of the hemorrhage. In three cases where patients were operated on 1 month after the hemorrhage, oculomotor functions did not recover.

Dexamethasone was used in the treatment of only 2 operated patients, who showed complete (1 case) and partial (1 case) regression of disorders after surgery.

**Cranial pain syndrome**, manifested as intense headaches, was observed in 81.6 % of cases within the first 24 hours after hemorrhage. These headaches persisted in 70 % of patients with hemorrhage history of up to one week.

In cases of slow disease development over a period of more than one month, headaches were not observed in 80.5 % of cases.

More rare cases include the development of severe vasospasm, with multiple ischemic foci in the basal ganglia developing in one case. Severe subcortical symptoms, including tremor, hyperkinesia, and severe dysarthria, were observed. In one case, static and coordination disturbances were noted. Emotional lability and depression were observed in two cases, fixational amnesia in one case, and decreased alertness to stupor and somnolence in five cases.

**Endocrinological disorders.** Pituitary insufficiency was observed in 34 (41.5 %) of 82 patients, and its incidence was quite uniform depending on the age of hemorrhage. Among these 34 patients with endocrinological disorders, the hemorrhage was less than 1 month old in 19 (55.9 %) patients, and in 15 of 34 (44.1 %) patients, hemorrhage was more than 1 month old.

It is important to note the irreversibility of pituitary dysfunction that we found when dexamethasone was not administered during the acute period of hemorrhage. Thus, of the 25 patients who did not receive dexamethasone, panhypopituitarism persisted during follow-up in 24 (96 %) patients. In contrast, regression of the disorder was observed in 8 of 9 (88.9 %) patients receiving dexamethasone from the time of diagnosis (Fig. 2). This difference was statistically significant (Fisher's exact test  $p < 0.05$ ).

Our experience has shown that one of the significant risks of emergency surgery is the inability to detect and preserve the remnants of the adenohypophysis in dense imbibed tumor tissue (Fig. 3).

Among 19 patients with pituitary insufficiency in the first month after hemorrhage, 7 underwent surgery, while 12 patients avoided it. Only 1 of the 7 (14.3 %) patients who underwent surgical treatment showed recovery

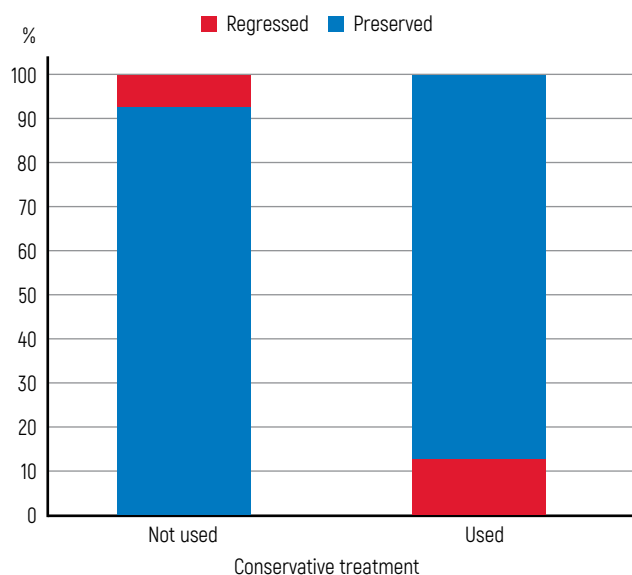
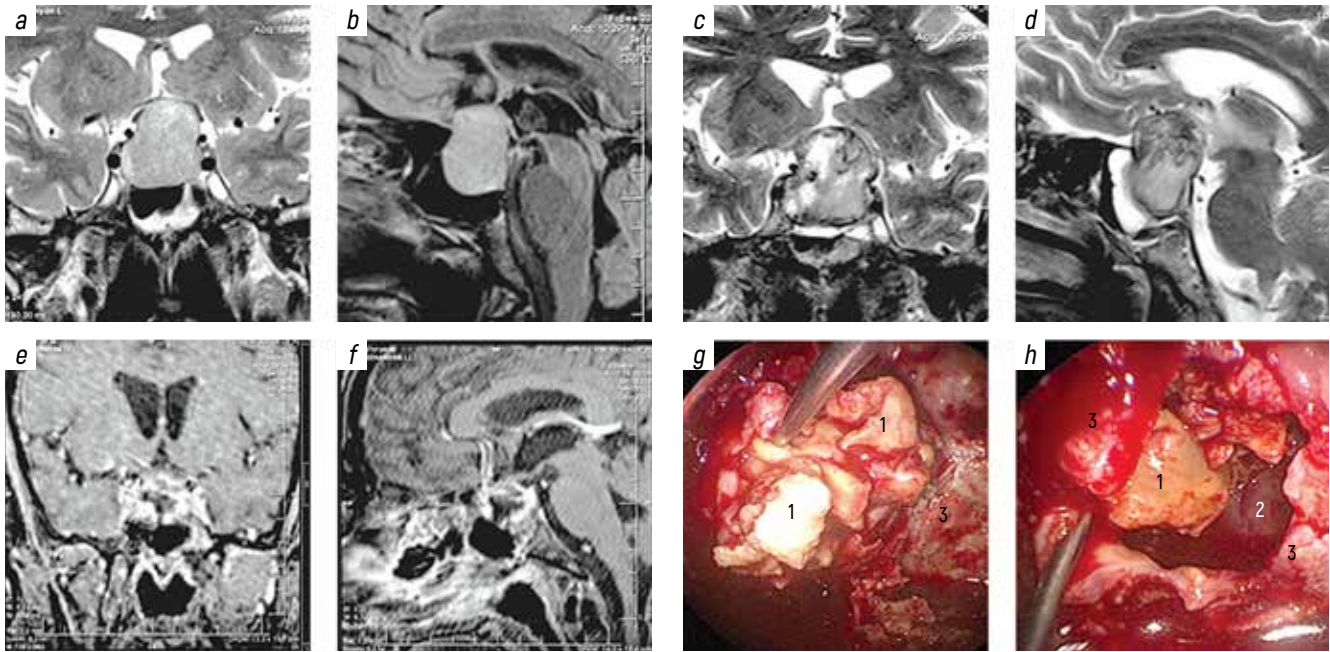


Fig. 2. Dynamics of pituitary abnormalities depending on the use of dexamethasone



**Fig. 3.** Clinical example of typical pituitary apoplexy with surgery performed 1 month after the hemorrhage. Patient, 56 years, underwent magnetic resonance imaging (MRI) several months after developing visual impairment which showed a typical pituitary tumor (a, b). Two months later due to physical exertion noted development of typical clinical manifestations of pituitary apoplexy: acute headache, nausea, vomiting, fast decrease of visual acuity. He was hospitalized 1 month after deterioration with bilateral amaurosis. MRI showed increase in tumor size, its stroma became heterogenous, edema of the sphenoid sinus mucosa developed (c, d). Tumor was resected through transnasal access. During surgery, the tumor was untypical yellow color, dense, hard to separate from dura mater (e, f). MRI 2 months after surgery showed complete tumor resection (g, h). Neurological status after surgery showed light perception in the right eye with continued amaurosis on the left. A course of electrostimulation of the optic nerves did not lead to further positive dynamics.

of pituitary function. In contrast, in patients with only conservative treatment without surgery in the first month after hemorrhage, the recovery of anterior pituitary function occurred in 50 % of cases (6 of 12 patients). However, this difference was not statistically significant.

**MRI characteristics of hemorrhage.** Because radiographic diagnosis of the disease in the vast majority of cases was performed not in our clinic but in various diagnostic centers, we used data from the most routine weighted magnetic resonance imaging (MRI) images (T1 without contrast and T2) to identify the radiographic characteristics of the hemorrhage depending on its age.

Indeed, other data were evaluated and used for diagnosis. The more detailed data of our analysis is presented in a previously published paper [32].

By examining the MRI data, we assessed the proportion of the tumor volume comprised by the hemorrhage area and whether the hemorrhage focus was a cyst or diffusely infiltrated tumor stroma. We also assessed the signal parameters of the hemorrhage area in routine MR imaging modes. We also described the changes of these parameters depending on the age of the hemorrhage (Table 2).

In early period after a hemorrhage, the site of the hemorrhage consists of blood-imbibed tissue, which then gradually develops into cystic cavities. Cysts begin to appear as early as one month after the hemorrhage, and after three months, the probability of detecting a cyst in the hemorrhage area reaches 80–100 %.

Morphological examination of the removed tumor reveals various changes in its stroma, from foci of necrosis and areas of connective tissue formation (scar tissue) to areas of unchanged (“live”) tumor. Example: Fig. 4. The morphological features of PA are discussed in more detail in our previously published work [43].

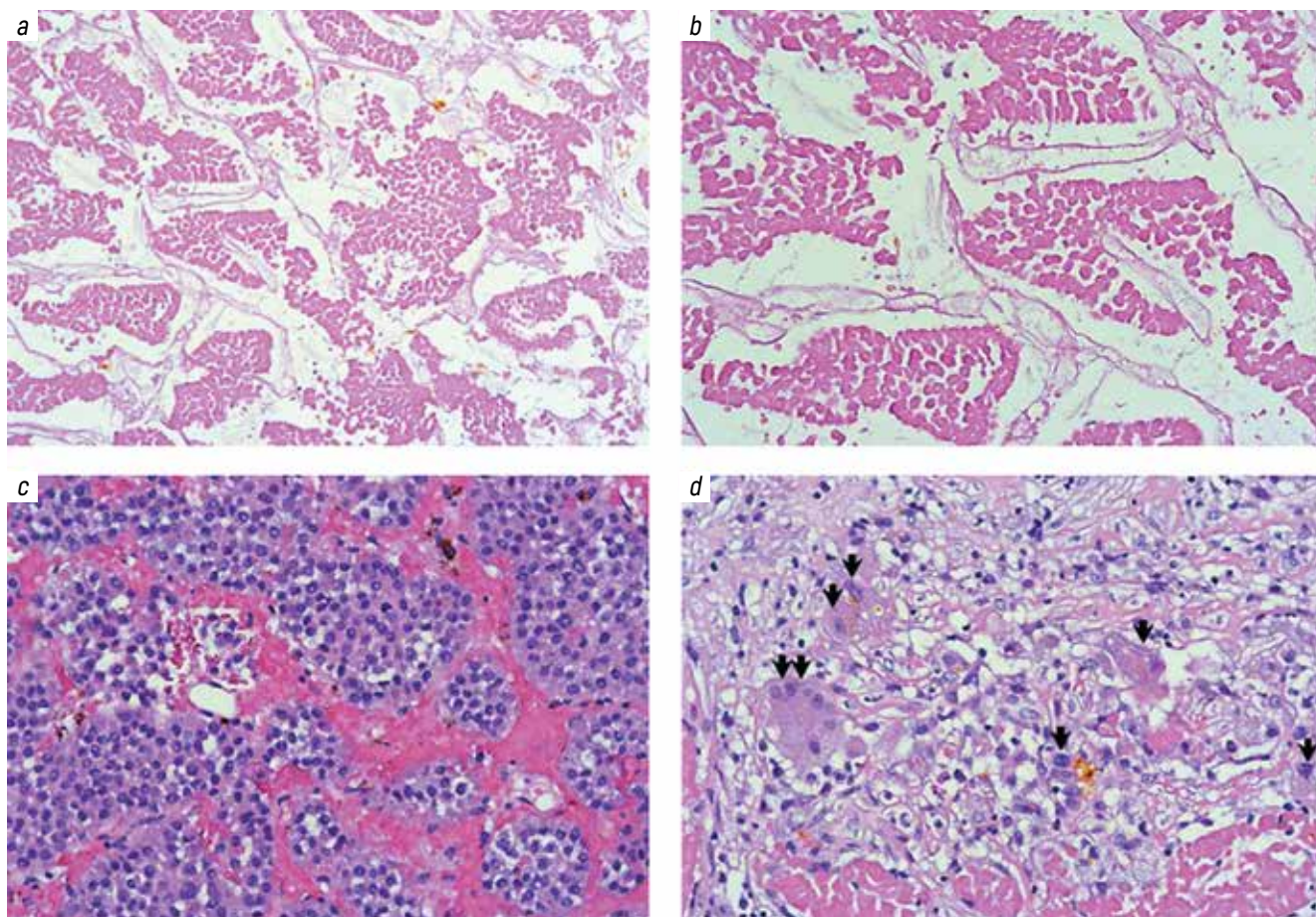
**Overview of the treatment methods used.** The surgical group included 45 patients operated on in our department using a transsphenoidal endoscopic approach [19, 28–31, 47]. This group turned out to be comparable in key indicators with a group of 37 patients who did not require surgery and in fact received only conservative treatment.

As a reminder, our indications for urgent surgery included hemorrhage into the tumor itself and the development of neurological deficits (chiasmal syndrome, oculomotor disturbances, cranial pain syndrome). However, not all acutely ill patients were hospitalized promptly to our department. These were the patients who comprised the conservative treatment group, and it was these patients who, by the time of hospitalization, no longer required surgery due to tumor resorption (see below).

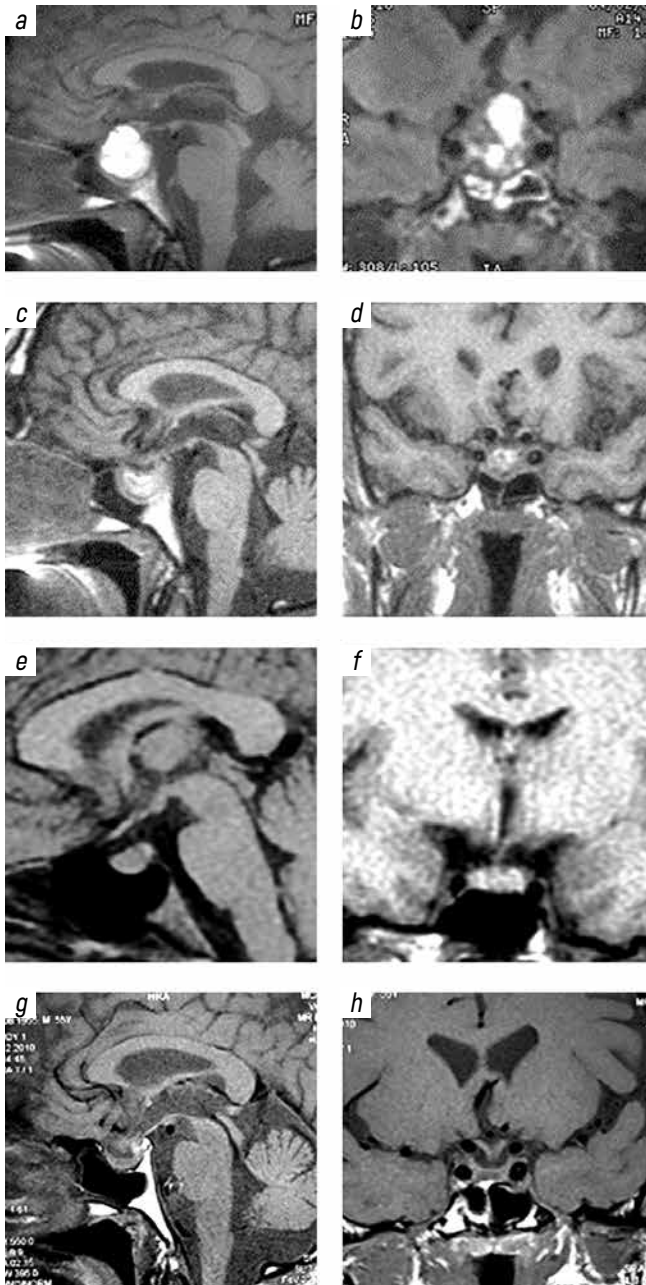
Tumor resorption, or more precisely, the resorption of hemorrhagic focus, is one of the most favorable outcomes following hemorrhage (Figs. 5 and 6). The non-operated group of patients primarily consisted of those with acute onset of events and early or routine diagnosis. Tumor resorption was detected in 89.2 % (33 of 37) of cases. We found that the probability of complete resorption for small

**Table 2.** MR characteristics of hemorrhagic focus in pituitary tumor at different times after hemorrhage

Time since hemorrhage	Number of observations, N	MR characteristics, abs. (%)	
		diffuse infiltration	presence of cysts
Up to 2 days	8	8 (100)	0
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	5 (100.00)
5–6 months	2	0	2 (100.00)
6–12 months	6	1 (16.67)	5 (83.33)
>12 months	12	0	12 (100.00)
<i>Total</i>	<i>82</i>	<i>44 (53.66)</i>	<i>38 (46.34)</i>



**Fig. 4.** Morphological changes during pituitary apoplexy: *a, b* – necrotic focus in the tumor tissue. No tumor cells are visible; *c* – a fragment of typical pituitary adenoma without signs of necrosis; *d* – area of necrotic focus organization: formation of fibrous bands and presence of giant cells which correspond to time from hemorrhage more than 2 weeks



**Fig. 5.** Example of tumor resorption after hemorrhage: *a, b* - MRI 7 days after hemorrhage; *c, d* - MRI 1 month after the start of conservative treatment; *e, f* - MRI 4 months after the start of conservative treatment; *g, h* - MRI 12 months after the start of conservative treatment

tumors (up to and including 25 mm in size) reaches 60 %, while for medium- and large-sized tumors (26–59 mm) it does not exceed 40 %.

The sizes of all tumors that underwent resorption in our series were less than 40 mm, and we use this value as the «threshold» when developing the treatment selection algorithm (see conclusion). Resorption of giant tumors (more than 60 mm) was not observed.

The probability of tumor resorption was higher when the hemorrhage site was represented by imbibed tumor

tissue [noted in 63.6 % (28 of 44) patients] than by a cyst [noted in 13.2 % (5 of 38)]. This difference was statistically significant (Fisher's exact test  $p < 0.05$ , chi-square  $< 0.001$ ). We did not observe resorption when the hemorrhage was more than 3 months old.

## DISCUSSION

**Representativeness of samples.** Traditionally, PA is considered as an indication for urgent surgery to decompress sellar and perasellar lesions [8, 9, 18–20, 33]. In most cases, improvement in vision and oculomotor functions is observed after surgery [23, 25, 48–51]. However, pituitary functions are not restored in the majority (up to 80 %) of patients [23–27].

Cases of spontaneous tumor resorption have been described in the literature [21, 22] with the possibility of preserving pituitary functions [23–27]. The results of conservative treatment of PA that we found were not inferior to urgent surgery in terms of the main indicators [24, 25, 52], especially when using dexamethasone as part of conservative therapy [53].

Previously, the general principles for the diagnosis and treatment of pituitary tumor hemorrhages were summarized by a group of British researchers, the Pituitary Apoplexy Guidelines Development Group, formed in February 2009 within the British Society of Endocrinologists. In May 2010, they formulated, and in 2011, published recommendations for the treatment of pituitary tumor hemorrhages – “UK guidelines for the management of pituitary apoplexy” [20].

The algorithm proposed by British colleagues is purely surgical in nature, ignoring tumor size, radiographic characteristics of the hemorrhage site, tumor hormonal activity, or even the age of hemorrhage. The patient's clinical condition, the severity of symptoms, and their dynamics were decisive in the choice of treatment method. Cases of spontaneous tumor resorption described in the literature were practically not reflected in the proposed recommendations. A more detailed analysis of the authors' recommendations was previously published by our group [41].

In our study, we were able to collect a group of patients with a classic «acute» onset of the disease, in whom the need for surgery had disappeared by the time of admission. This was facilitated by a number of circumstances beyond our control, delaying admission to hospital long enough for patients, as their condition improved, to undergo repeat MRI, which demonstrated tumor resorption. A detailed analysis of this group of patients allowed us to reexamine our understanding of PA and propose the following diagnostic and treatment algorithm for such patients.

Firstly, the dependence of treatment outcomes on the severity of the event is clear. In the surgical group, the course of events was generally subacute or gradual, with the occurrence of hemorrhage being diagnosed by MRI and confirmed by surgical findings. Patients had no history of acute deterioration of their condition, and most of them

had intact pituitary function at the time of admission, despite not receiving dexamethasone preoperatively.

In contrast, in patients with acute development of events, the severity of clinical manifestations and the rate of their development were such that the moment of onset of the disease was almost always remembered by them, the severity of the condition required contact with medical institutions and treatment, and by the time of referral to our center, tumor resorption and persistence of pituitary insufficiency were observed simultaneously in the absence of the use of dexamethasone in the early stages of hemorrhage.

The ability for quickly and effectively decompression of the optic and oculomotor nerves is a clear argument in favor of surgery. However, the likelihood of improvement decreases as the duration of preoperative period increases. Optimally, surgery should be performed no later than one month after the hemorrhage.

Unfortunately, when performing such surgeries at such an early stage, it is extremely difficult to detect and preserve the remnants of the adenohypophysis within dense imbibed tumor tissue. Almost no one patient undergoing emergency surgery has experienced recovery of pituitary function.

During follow-up, the regression of pituitary dysfunction was observed in only 27.3 % of patients operated on within the first week after hemorrhage, compared to the group of non-operated patients, in whom restoration of anterior pituitary function occurred in 87.5 % of cases. This result can be considered as a counterargument against urgent surgical treatment, especially in the absence of visual and/or oculomotor impairments.

An analysis of treatment outcomes for not operated patients because of various reasons demonstrated the potential for recovery of visual, oculomotor, and hormonal disturbances during conservative treatment, as well as the potential for complete tumor resorption. In other words, wait-and-see strategy and conservative therapy in some cases provide treatment outcomes comparable to those of surgery. The use of dexamethasone significantly improves the outcomes of both surgical and conservative treatment in the acute phase.

Thus, in addition to the generally accepted strategy of performing surgery as quickly as possible from the moment the clinical signs of PA appears, for patients with a hemorrhage history of less than 3 months, a maximum tumor size of 40 mm with the focus of hemorrhage as imbibed tissue and not a cyst, and minimal visual and oculomotor impairments, a wait-and-see strategy can be recommended, which can provide a result comparable to surgical treatment and even superior to it in terms of preserving pituitary functions.

If there is no improvement despite conservative treatment, the nature of the disease must be clarified. A differential diagnosis must include craniopharyngiomas, dermoid cysts, aneurysms, and other pathologies.

Indeed, we only assume that the mass in the sella turcica detected by MRI during the deterioration of the

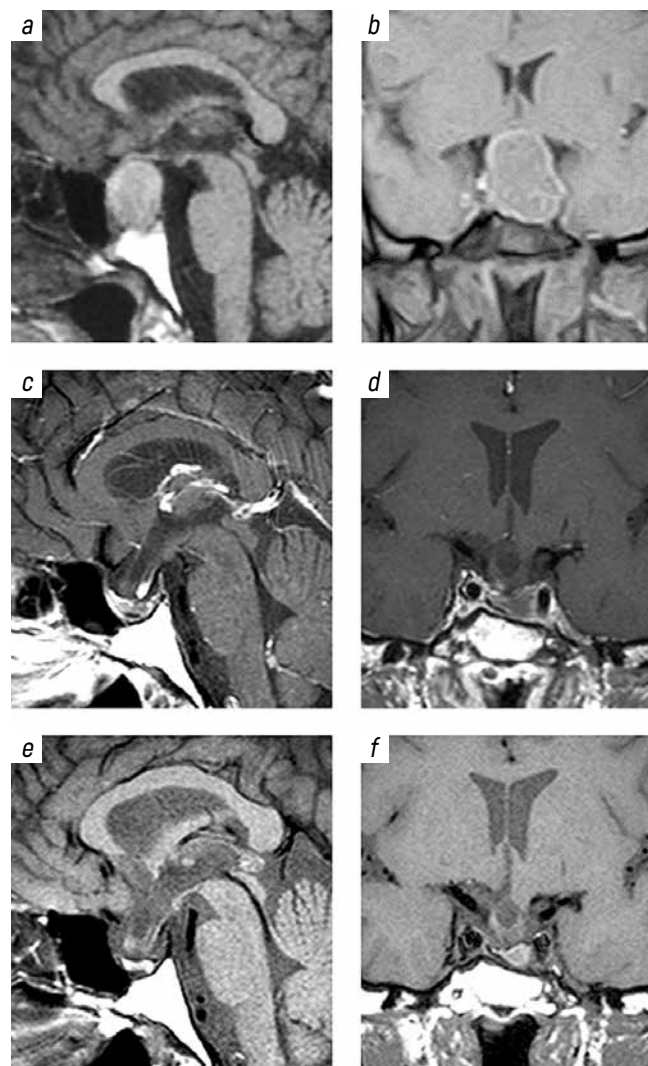
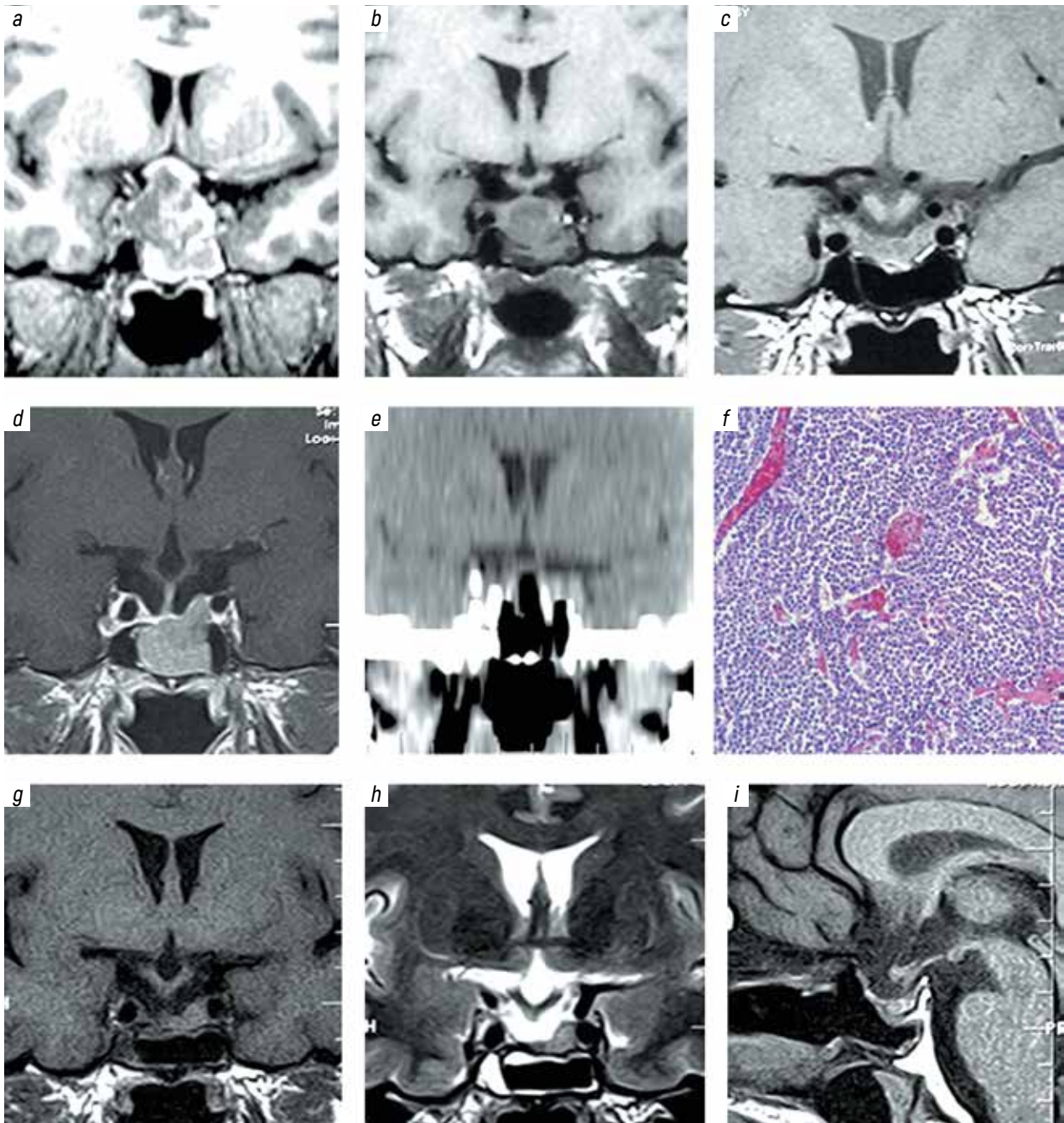


Fig. 6. Example of tumor resorption after hemorrhage: *a, b* – MRI 10 days after hemorrhage into pituitary tumor; *c, d* – MRI 2 months after the start of conservative treatment; *e, f* – MRI 7 months after the start of conservative treatment

patient's condition is a pituitary tumor with hemorrhage into its stroma. In the vast majority of cases, these patients had not previously undergone MRI and were unaware of the pathology. Only patients with prolactinomas had a baseline MRI, and the presence of a tumor was clearly present in these patients (see Fig. 6).

The results of the morphological examination of the sella turcica contents in the operated group confirmed our assumptions, which, in turn, allowed us to similarly evaluate the clinical data in the unoperated patients. The detection of an empty sella turcica with a preserved anterior pituitary gland in dynamic MRI allowed us to confirm tumor, or more precisely the hemorrhage, resorption.

The case of a recurrence of a pituitary tumor in a patient with a “classic” PA scenario only confirms the above assumptions, as well as the very fact that there was initially a pituitary adenoma, and not another lesion (Fig. 7).



**Fig. 7.** Clinical example of recurrent pituitary adenoma after pituitary apoplexy. Patient, 26 years, in 2010 survived an episode of severe headache, nausea and vomiting, decreased visual acuity. He was hospitalized into a neurological department of a city hospital. MRI performed on day 2 showed endo-supra-infrasellar neoplasm (a). During dexamethasone injections and replacement therapy. MRI 2.5 months later showed significant decrease in tumor size (b). MRI 8 months after apoplexy showed complete tumor resorption (c). The patient did not undergo MR controls for 11 years. He performed control due to headache, learned of tumor recurrence (d). CT control immediately after surgery showed complete resection of the tumor through transnasal access (e). MRI control 2 months later confirmed complete resection (e-h). Microscopic tumor - typical pituitary adenoma (i): the specimen consists of tumor fragment of solid structure with round cells with round nuclei, eosinophilic cytoplasm, rare perivascular structures

It is also important to consider the assumption that we were able to observe the “full” spectrum of “acute” situations and there are very few cases where patients do not survive a hemorrhage without treatment and are not observed by us. That is, the “true” situation is statistically indistinguishable from our results.

#### CONCLUSION

Our analysis of treatment outcomes for both surgically treated patients and those with conservative treatment demonstrates that PA is a serious complication of a benign condition. The severity of the symptoms, rapid deterioration of the patient’s condition, and the development

of neurological symptoms as well as endocrine insufficiency determine the indication for urgent neurosurgery.

However, in cases where, for a number of reasons, the patient was not operated on within the first 10–14 days

from the onset of the first deterioration symptoms, it makes sense to clarify the indications for surgery due to the fact that there is a possibility for spontaneous tumor resorption, confirmed by the results presented in the article.

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M.A. Kutin, P.L. Kalinin: study concept and design, manuscript writing, approval of the official manuscript version, consent to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work would be appropriately investigated and resolved; B.A. Kadashev: study design, introduction of significant (important) revisions to increase scientific value of the article, approval of the official manuscript version, consent to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work would be appropriately investigated and resolved;

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