Original article

Ukr Neurosurg J. 2023;29(4):13-21
doi: 10.25305/unj.286547

Endoscopic endonasal surgical management of giant pituitary adenomas with extension into ventricle system

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Received, 29 August 2023
Accepted, 02 October 2023

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Objective: to estimate the results of endoscopic endonasal surgical management of giant pituitary adenomas (GPAs) with extension into ventricular system (VS), to study the peculiarities of surgical techniques.

Materials and methods. 49 adult patients with GPAs with extension into VS were included in the study. The depth of research 2016-2021. This is a consecutive sampling of 1339 pituitary adenomas. GPAs with extension into VS made up 3.66% (49/1339) among all treated pituitary adenomas, and 43.4% among 113 GPAs. Distribution by gender – 18 (36.7%) women and 31 (63.3%) men. Average age was 54.1±11.3 years.

Results. The largest consecutive series of GPAs with extension into VS that underwent endoscopic endonasal surgery was analyzed. Gross total resection was achieved in 32.7% (16/49), subtotal – 42.9% (21/49), partial – 12.2% (6/49), contraindications for tumor removal were issued in 12.2% (6/49) cases, these patients underwent extended biopsy and ventriculoperitoneal shunting in 4 patients. In 67.4% (33/49) was admitted visual function improvement. In 12.2% (6/49) vision remained at preoperative level, with no visual impairment. In 20.4% (10/49) of cases, vision deteriorated immediately after surgery. Upon re-examination at 6–8 weeks in this group, vision returned to baseline in 60% (6/10) of patients. An immunohistochemical study found that 89.8% of the tumors were hormonally inactive. There was allocated a separate group of null cell pituitary adenomas, which accounted for 18.9% of cases. ACTH, LH-FSH, GH, TTH, prolactin secreting PAs were detected in 30.6%, 24.5%, 16.3%, 8.2% and 2.0% respectively. Hypopituitarism was diagnosed in 30.6% (15/49) of patients. Diabetes insipidus was detected for the first time in the postoperative period in 12.2% (6/49) of patients. 14.3% (7/49) of the cases of postoperative cerebrospinal fluid leak were diagnosed. Meningitis developed in 8.1% (4/49). The mortality rate was 6.1% (3/49).

Conclusions. An analysis of complications in the early postoperative period found that the incidence of complications in GPAs with extension into VS was statistically significantly higher when compared to the cohort of patients who underwent endoscopic endonasal surgery for pituitary adenomas removal, indicating the complexity of this pathology. Despite the significant increase in the complexity of endoscopic interventions and still considerable threats of postoperative cerebrospinal fluid leak in the opening of the VS, we can already consider endonasal operations in the vast majority of GPAs as the method of choice. A new classification approach to the study group of GPAs was proposed. It allows us to separate the relatively low-risk and high-risk groups of high-flow intraoperative cerebrospinal fluid leak, which is directly correlated with the risks of postoperative complications and mortality in our study. In addition, we emphasize a special, although the smallest group of GPAs with extension into the third ventricle (type 3). Such cases require special attention and the decision to have ventriculoperitoneal shunting before or immediately after the removal of the tumor.

Key words: *giant pituitary adenoma; ventricle system; endoscopic endonasal surgery*

Introduction

Pituitary adenomas (PA, PitNET according to the new classification) are benign space-occupying masses [1] with a prevalence of 10–15% among all intracranial tumors [2]. Giant pituitary adenomas (GPAs) represent a complex neurosurgical pathology often associated with invasive tumor growth into the parasellar structures [3]. GPA is conditionally defined, most commonly with a criterion of ≥40 mm in any plane on magnetic resonance imaging (MRI) [4]. The literature reports a prevalence

of GPA in 6-10% of patients diagnosed with pituitary adenomas, with some authors reporting up to 14% [5]. In cases with significant suprasellar spread, GPAs can extend into the third ventricle, as well as the anterior horns of the lateral ventricles, which complicates their surgical removal, due to the narrow surgical corridor created by the proximity of anatomical structures. In the literature, there are data on individual clinical cases or small series of GPA with extension to the area of the third ventricle or anterior horns of lateral ventricles, which makes it impossible to determine the prevalence of this pathology [6–8]. There are few references to a significant analyzed series of such tumors in the literature.

In Ukraine, the problem of surgical treatment of GPA was studied by Yaroslav V. Patsko According to the results of the dissertation research "Pituitary adenomas with extensive extrasellar spread" (1987), out of 422 patients, in 191 PA had significant suprasellar spread. 19 cases of spread to the third ventricle are described. The case fatality rate in this study (overall for PA with significant extrasellar spread) was 26.7% (51/191) [9]. In the dissertation of O.V. Maidannyk, devoted to the surgical treatment of GPAs (2015), all tumors were operated either microsurgically transsphenoidally or transcranially, and cases of intraventricular spread were not mentioned [10]. In the thesis of M.O. Guk " Diagnosis and comprehensive treatment of hormonally inactive pituitary adenomas" (2017) showed a statistically significant increase in the risks of surgical treatment and postoperative mortality in the presence of hydrocephalus in patients with GPA [11].

Currently, the transition to endoscopy in the surgery of PAs and other tumors of sellar and parasellar localization is being completed worldwide. The advantage of endoscopic endonasal surgery (EES) is better visualization and the possibility of radical tumor removal outside the narrow "sellar" surgical corridor [12]. In Ukraine, the first patient with GPA with spread to the third ventricle was operated on using an extended endonasal transsphenoidal transtubercular approach in 2016.

Objective: to analyze the results of surgical management of giant pituitary adenomas with extension into ventricular system using endoscopic endonasal surgery, to study the peculiarities of surgical intervention techniques.

Materials and methods

Study participants

A consecutive sample of pituitary adenomas 1,339 operated on from 2016 and 2021 was analyzed.

The study group involved 49 adult patients with GPAs with extension into ventricular system (VS), operated on in the department of endonasal neurosurgery of the skull base of the State University Romodanov Neurosurgery Institute NAMS of Ukraine in the period from 2016 to 2021.

Informed and voluntary written consent to participate in the study was obtained from all patients.

The study was approved by the Committee on Ethics and Bioethics of the State University "Institute of Neurosurgery named after Acad. A.P. Romodanov of the National Academy of Sciences of Ukraine" (Minutes No. 5 dated December 13, 2019).

Inclusion criteria

1. Tumor sizes ≥40 mm in any plane according to MRI data.
2. Patients underwent endoscopic endonasal surgery (EES).
3. Tumor extension into the third ventricle and/or anterior horns of the lateral ventricles.
4. Histologically confirmed pituitary adenoma.

Characteristics of the group

There were 18 (36.7%) women and 31 (63.3%) men in the study group. The average age of patients was 54.1±11.3 years. The youngest patient was a 19-year-old man at the time of treatment, the oldest was a 78-year-old man. The average age of both genders differed slightly and was 54.3±9.0 and 54.0±12.1 for women and men, respectively.

The share of GPAs with extension into the VS was 3.66% of all treated PAs (49/1339) and 43.4% of 113 GPA cases. 75.5% (37/49) of GPAs were operated on initially, and reoperation following microsurgical endonasal removal was performed in 24.5% (12/49).

Endoscopic endonasal transsphenoidal transtubercular transplanar removal of PAs of different degrees of radicality was performed in 43 (87.8%) patients. In 6 (12.2%) patients due to continued growth, size >60 mm, previous radiosurgical treatment of the tumor, an extended biopsy was performed, in 4 patients a ventriculoperitoneal shunting was installed to eliminate hydrocephalus.

Catamnesis was 54.2±20.5 months (from 86 to 21 months).

Study design

The study is retrospective.

Diagnostics

GPAs with significant suprasellar extension is characterized by volumetric impact on the optic nerves and pituitary stalk. Preoperative diagnosis should be based on a multidisciplinary approach [13]. Given the involvement of the optic and oculomotor nerves, patients should be examined by a neuro-ophthalmologist to determine the visual acuity, the state of the ocular fundus using fundoscopy, assessment of visual fields using computer perimetry, and, if necessary, determination of the condition of the retina and optic disc using optical coherence tomography. The majority (39 (79.6%)) of patients sought medical help due to the manifestation of visual disturbances (decreased visual acuity as the only clinical manifestation or in combination with narrowing of visual fields (29 (59.2%) cases) and diplopia (3 (6.1%)). In 36 (73.5%) patients headaches were also reported, however, this symptom is not specific for GPAs and pituitary adenomas in general [14].

At the stage of hospitalization, 17 (34.7%) patients were diagnosed with hypopituitarism according to laboratory screening of pituitary hormone levels. In most cases (44 (89.8%)), GPAs turned out to be non-functioning

This article contains some figures that are displayed in color online but in black and white in the print edition

adenomas, which was confirmed by immunohistochemical examination, however, they could entail hypopituitarism due to their volumetric effect. Among non-functioning PAs, 9 (18.9%) were null-cell, i.e. no adenohypophyseal differentiation was found in them [15]. In the presented series, the share of null-cell PAs was 18.9% (5), which is a significantly higher prevalence rate (compared to 0.6% among non-functioning pituitary adenomas in the population of patients with diagnosed PAs ($p<0.001$)) [16]. Preoperative examination by an endocrinologist makes it possible to identify neuroendocrine disorders for further correction, which reduces the risk of peri- and postoperative endocrine complications. Endocrine disorders in the form of amenorrhea, acromegaly, and weight gain were observed in 2 (4.1%) patients.

MRI of the pituitary gland with intravenous contrast remains the standard for visualization of a volumetric mass, which gives an idea of involvement of parasellar structures [17]. According to neuroimaging studies, 27 (55.1%) patients were diagnosed with liquor-dynamic disturbances in the form of occlusive symmetric or asymmetric hydrocephalus of varying severity.

When comparing data from a neuroophthalmologist's examination, MRI of the pituitary gland, and intraoperative data, the dependence of spread of suprasellar part of the tumor on the location of the chiasm was found. According to the literature, there are three positions of the chiasm: anterior, central, and posterior. With the central position, found in 70% of autopsies, the chiasm is located above the sella turcica, the anterior (the chiasm is located closer to tuberculum sellae) and the posterior (the chiasm is located closer to the dorsum of the sella turcica) position is in 15% of cases [18]. Considering the fact that most patients had a long history of the disease before manifestations of ophthalmological disorders, PA, spreading suprasellarly, bypassed the optic nerves or tracts. ***Fig. 1*** schematically depicts possible variants of significant suprasellar spread of GPA depending on the position of the chiasm.

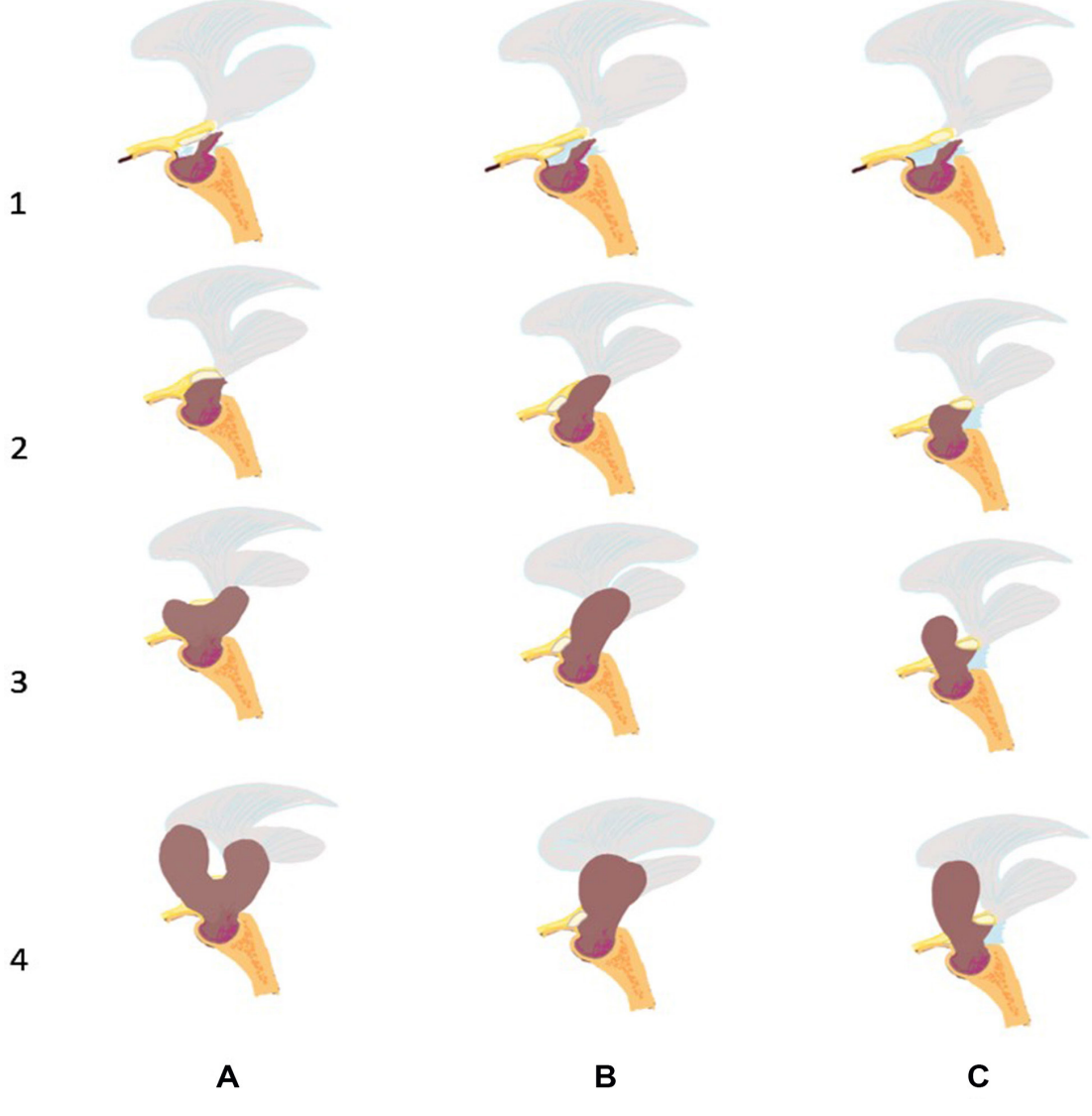

Fig. 1. Variants of tumor extension depending on the chiasm position: A – central chiasm position; B – anterior chiasm position; C – posterior chiasm position; 1 – the tumor is located endosellarly; 2 – the tumor extends supradiaphragmally to the level of the chiasm; 3 – the tumor extends to the ventricular system, compressing the chiasm; 4 – the tumor extends into the ventricular cavity

Thus, the dominant symptom in patients with GPAs with extension to the VS is a decrease in visual acuity.

All patients underwent histological verification and immunohistochemical examination.

Surgical management

For significant suprasellar spread, extended endonasal endoscopic transtubercular/transplanar (EETT) approaches should be used. According to D. Mazzatenta, the use of EETT approach is "inevitable" for tumors requiring transcranial removal [19].

The approach is performed in the supine position with 15° rotation of the head to the right and 10° extension. This head position allows achieving the projection of the third ventricle along a straight trajectory and reducing the angle of attack for the part of the tumour spreading into the anterior horns of the lateral ventricles. Vasoconstriction and adrenalization of the nasal passages mucosa are mandatory for better visualization of the structures and widening of the surgical corridor. Surgical manipulations are performed in 4 hands. 0° endoscope is used at the stages of formation of the nasoseptal flap, bone window, during removal of the endoinfrasellar part of the tumor. The nasoseptal flap is formed in all cases at the access stage. Preserving the sphenopalatine artery in the flap structure is an important condition for postoperative healing of the mucous membrane. When the sphenopalatine artery is damaged in the postoperative period, partial or total necrosis of the nasoseptal flap may occur [20]. When the main sinus is large, nasoseptal flaps can be formed in both nasal passages during the access stage. During the plastic reconstruction stage, the "best" flap is chosen, covering the bony defect and extending beyond the bone window.

Standard endoscopic endonasal transsphenoidal approach with extended sphenoidotomy is used to access the sella turcica. Visualization of both opticocarotid recesses and identification of the C_{5-}segment of the internal carotid artery on both sides using intraoperative Doppler ultrasonography is a prerequisite for the formation of a sufficient bony window and safe dissection of the dura mater. High-speed diamond burs with fine dusting under constant irrigation are used to thin the bones of the fundus and tubercle of sella turcica, a wedge-shaped protrusion. The specified structures are resected using Kerrison bone punches (USA). We do not use a chisel to maintain atraumatic access. Often, the fundus of the sella turcica is thinned due to prolonged volumetric effect of the tumor or its infrasellar spread. Excision of the dura mater is performed using straight and/or 30° angled endoscopic microscissors. Tumor removal occurs in several stages. The first stage involves endocapsular removal of the endo-infrasellar part of the tumor using aspiration and curettage, depending on the stromal density. In cases of parasellar extension, removal from the area of the cavernous sinuses is primarily performed using curettage. During the removal of the suprasellar part of the tumor, the technique of 2 aspirators (Fukushima 12Fr L and Fujita 12Fr L, Japan) is used. If the stromal density is high, curved pituitary rongeurs can be used additionally. Curettage of the suprasellar part of the tumor without visual inspection may result in premature CSF leakage from the suprasellar cistern. Active aspiration of the cerebrospinal fluid through the lumbar drainage plays a special role in the removal of the suprasellar portion of PA (established at the preoperative stage). During endocapsular removal, the suprasellar cistern can descend into the bed of the removed tumor and cover the operative field. To relax the suprasellar cistern and reduce intracranial pressure, it is possible to use intravenous mannitol infusion at a dose of 0.5 g/kg of body weight, active aspiration of cerebrospinal fluid up to 10 ml, and hyperventilation using artificial lung ventilation. This manipulation allows reaching the area of the third ventricle and the anterior horns of the lateral ventricles. In case of soft tumor consistency, it is most often squeezed into the bed of the removed part by the suprasellar cistern. When reaching the area of the third ventricle and/or the anterior horns of the lateral ventricles, 30° and 45° optics should be used for adequate visualization. During manipulations on the suprasellar part of the tumor, the classical arrangement of the instrument (endoscope – according to number 12 of the conventional dial, the instrument – according to numbers 5 and 7) is changed to inverted one (endoscope – according to number 6, instrument – according to numbers 11 and 1) **(*Fig. 2*)** .

When the distal pole of the tumor is removed, high-flow cerebrospinal fluid leak from the VS (3rd degree) occurs ***(Fig. 3)*** [21].

The tumor capsule is usually represented by the distended pituitary gland, the diaphragm of sella turcica, and the arachnoid membrane. If pituitary cells can be identified, the pituitary remnant is not removed to preserve endocrine function. When reaching the ventricular cavity and having no capsule, the tumor is removed completely.

Given the presence of high-flow cerebrospinal fluid leak from the ventricular cavity and connection to the nasal cavity, multi-layer plastic surgery using autologous and artificial materials is performed to close the postoperative defect. The defect of the ventricle is covered with collagen matrix TachoComb® (Takeda, Japan), the cavity of the removed tumor is lined with a hemostatic material and filled with a fragment of fat from the thigh or the anterior abdominal wall. A fragment of the fascia lata is lined under the bone (inlay plasty). The nasoseptal flap is lined on the posterior wall of the sphenoid sinus. A hemostatic sponge (Surgispon®, Aegis Lifesciences, Thailand) and nasal dressings (Merocel®, Medtronic, Ireland) are used to achieve tight adhesion of the flap to the bone.

Complications

Extended endoscopic endonasal approaches are associated with intraoperative CSF leak, because such approach involves invasion into the suprasellar cistern. In combination with extension into the VS, with total and subtotal removal, high-flow cerebrospinal fluid leak occurs in all cases. With partial removal or biopsy, patients with hydrocephalus have increased intraventricular CSF pressure. The ventriculoperitoneal shunting was installed in 33.3% (4 out of 12) of patients to eliminate hydrocephalus.

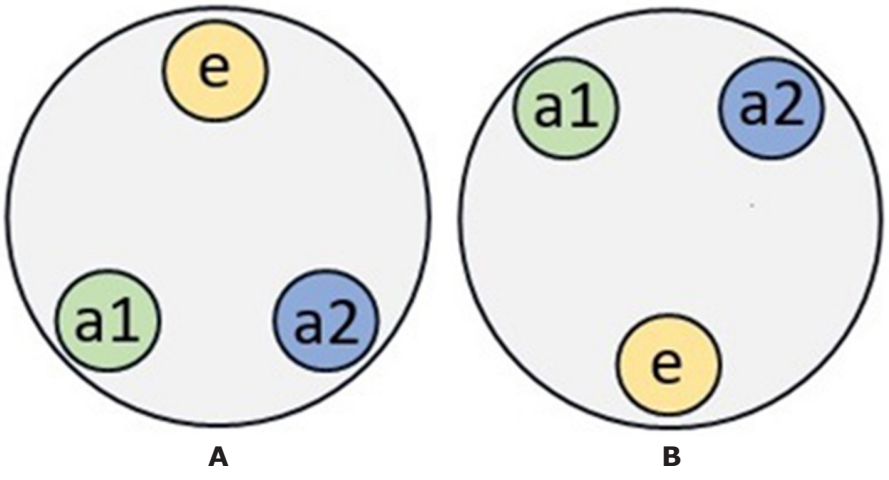

Fig. 2. Position of the endoscope and surgical instruments in the surgical wound: A – classic position; B – position during removal of the suprasellar part using angled optics (e – endoscope; a1 – aspirator 1; a2 – aspirator 2)

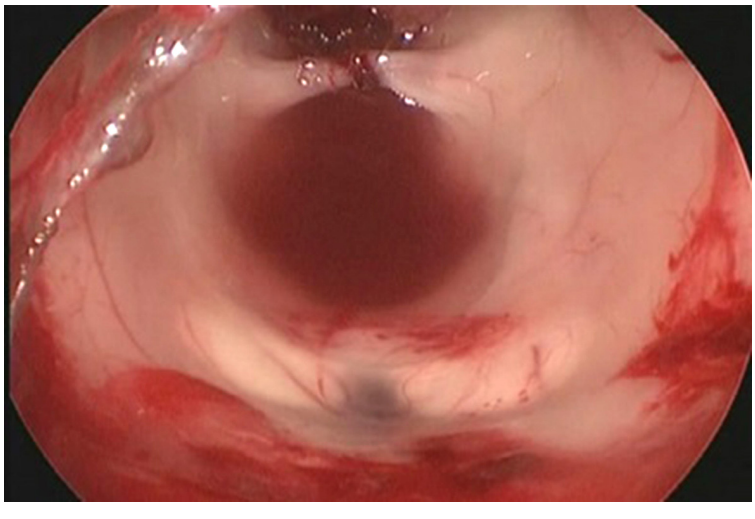

Fig. 3. Intraoperative visualization of the cavity of the third ventricle after giant pituitary adenoma removal

Intraoperative CSF leak in some cases can lead to the accumulation of air in the cranial cavity intradurally and, as a consequence, during the creation of a valve mechanism or long-term uncontrolled postoperative drainage of cerebrospinal fluid with the help of lumbar drainage, patients may develop tension pneumocephalus in combination with cerebrospinal fluid hypotension. This complication was not observed in our series, but has been described in the literature [22].

Manipulations on the tumour, especially when it is devascularised, result in impaired microcirculation. In cases of manipulation of the optic nerves and chiasm, patients may experience a short-term decrease in visual acuity. Coagulation of the tumor capsule or blind manipulation in the area of the pituitary stalk may induce diabetes insipidus [23].

Due to the installation of nasal dressings in the nasal passages in the early postoperative period, airway obstruction occurs, which, combined with mucosal edema, increases the cephalic syndrome, which mostly disappears after their removal.

Statistical analysis

Student's t-test for unrelated groups was used to assess the probability of differences (p) in the indicators of independent groups. A difference of $p<0.05$ was considered statistically significant.

Results

In the presented surgical series, all pituitary adenomas had endo-suprasellar spread, 18 (36.7%) - infrasellar, 15 (30.6%) - parasellar, 12 (24.5%) - antesellar, 6 (12.2%) – retrosellar ***(Fig. 4)***.

All patients underwent repeated ophthalmological examination. In the early postoperative period, 33 (67.4%) patients showed improvement of visual function (increased visual acuity and widening of visual fields), 6 (12.2%) had vision that remained at the preoperative level, there were no visual disturbances, 10 (20.4%) - vision worsened immediately after surgery, but at re-examination after 6-8 weeks in this group, vision was restored to the previous level in 6 patients.

Hypopituitarism remained at the preoperative level in 15 (30.6%) patients, hypopituitarism developed in 1 patient due to tumor removal in the early postoperative period, and in 1 patient it regressed.

Diabetes insipidus as a result of removal of GPA spreading to the VS was first diagnosed in the postoperative period in 6 (12.2%) patients.

R. Stefanidis et al. (2022) conducted a systematic review of postoperative complications in pituitary adenoma surgery and reported 9.2% incidence of hypopituitarism in a sample of 110 surgical endoscopic cases (p=0.009). Diabetes insipidus was first detected in 12.2% of patients (p=0.049) [24].

In the postoperative period, CSF leak occurred in 7 (14.3%) cases. According to B.D. Thorp et al. (2014), in a series of 152 cases, the incidence of postoperative CSF leak was 3.3%, in patients with GPA, this rate was statistically significantly higher than in a series of endoscopic endonasal surgical management of PA (p=0.024) [25]. Six out of seven patients with postoperative CSF leak were on lumbar drainage until the closure of the CSF fistula, 5 of them had lumbar drainage for more than 7 days, 1 patient had the drainage removed on the 5th day, and 1 patient underwent plastic revision of the defect.

Meningitis developed in 4 (8.1%) cases, which is statistically significantly more frequent compared to the incidence of bacterial meningitis in the cohort of patients who underwent transsphenoidal removal (p<0.001) [26]. Meningitis was combined with CSF leak in 3 (6.0%) cases, and in 1 patient meningitis occurred without CSF leak.

The mortality rate was 6.1% (3 patients out of 49): 1 - due to intraventricular hemorrhage, 1 died from purulent meningitis, 1 died from pulmonary embolism.

The average duration of surgery was 227.9±74.9 min.

The average length of hospital stay was 14.9±4.6 days.

Gross total resection was achieved in 16 (32.7%) patients, subtotal removal in 21 (42.9%), partial removal in 6 (12.2%). Contraindications to tumor removal were established in 6 (12.2%) cases ***(Fig. 5)***. These patients underwent extended biopsy, and ventriculoperitoneal shunting was installed in 4.

According to the results of an immunohistochemical study, 89.8% of tumors were non-functioning. Null-cell PAs (18.9% of cases) were allocated to a separate group.

Among the removed tumors of PA that secreted adrenocorticotropic, luteinizing/follicle-stimulating, somatotropic, thyroid-stimulating and prolactin hormone was found in 30.6%, 24.5%, 16.3%, 8.2% and 2.0% of cases, respectively ***(Fig. 6)***.

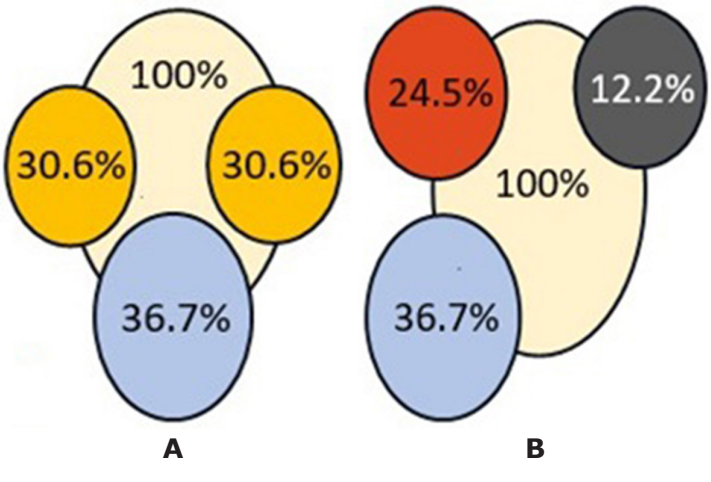

Fig. 4. Schematic representation of pituitary adenoma extension relative to the sella turcica in percentage. Endo-suprasellar location is marked in beige, parasellar in yellow, infrasellar in blue, antesellar in red, retrosellar in black; A – coronal plane; B – sagittal plane

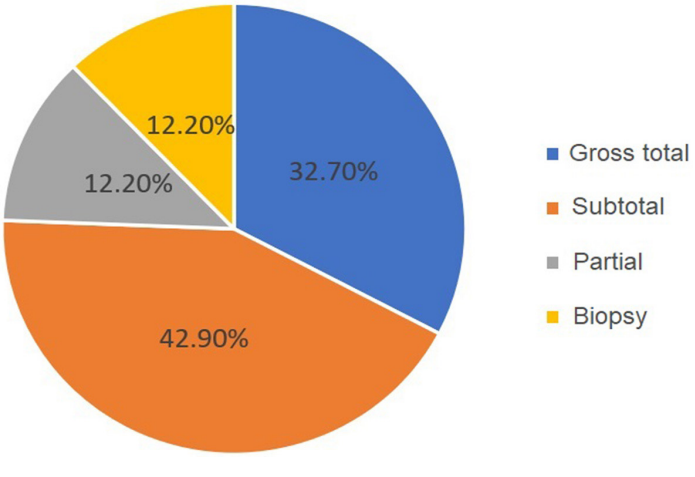

Fig. 5. Distribution according to radicality of GPA removal

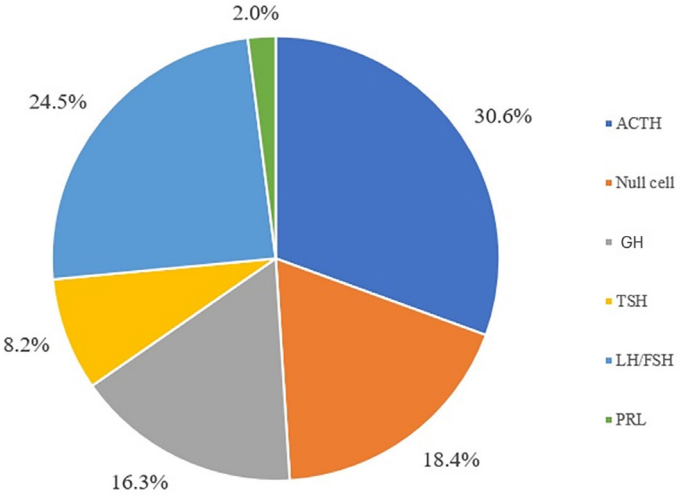

Fig. 6. Distribution of GPA according to immunohistochemical study results

Discussion

When creating anatomical classifications, the authors focused on the tumor correlation with cavernous sinuses and carotid arteries (Knosp classification), the degree of invasion of the sella turcica and suprasellar extension (Hardy classification), tumor size, its position relative to the sella turcica and the chiasm, as well as the dependence on the invasion of parasellar structures (Yasargil classification), the form of GPA (Berkman classification) and the extension of PA in 5 directions with a score gradation of the degree of spread (SIPAP classification). These classifications were created to determine the extension of PA according to MRI data at the preoperative stage. They are widely used in clinical practice by radiologists. Among the given classifications, only Hardy singled out type C for suprasellar growth, during which the tumor extends into the third ventricle, reaching the foramen of Monro. According to SIPAP classification, grade 4 extension is associated with significant suprasellar tumor growth, which leads to occlusive hydrocephalus due to compression of the foramen of Monro. Thus, it can be argued that there is currently no classification that would reflect the degree of involvement of the ventricles of the brain with significant suprasellar extension.

Due to the absence of GPA classification, we have developed a classification for GPA extension into the VS, which allows determining the volume and the need for plastic surgery of the postoperative defect at the preoperative stage.

The classification is based on MRI data and multispiral computed tomography (with intravenous contrast) indicating the involvement of the VS in GPA: type 0 – no interaction with the ventricles of the brain, 1 – adherence to the ventricles (third and lateral) with their compression or deformation, 2 – extension into the ventricular cavity, 3 – extension into the ventricular cavity with blockage of the foramen of Monroe and/or hydrocephalus ***(Fig. 7)***.

Rationale for classification: type 1 – when adjacent to the brain ventricles, the risk of postoperative cerebrospinal fluid leak from the VS is minimal; type 2 – when spreading into the ventricular cavity, the risk of cerebrospinal fluid leak is high, but it depends on the eradication of the tumor and the thickness of capsule at the point of contact with the ventricular cavity; type 3 - two options are possible: a) no radical removal - installation of ventriculoperitoneal shunting to correct asymmetric or symmetric hydrocephalus, there is no cerebrospinal fluid leak; b) radical removal, resulting in high-flow cerebrospinal fluid leak from the ventricle.

Conclusions

Treatment of GPA remains challenging. The extension of GPA into the third ventricle occurs mainly in late diagnosis of the disease. This is attributed to the presence of clinically non-functioning variants of PA, in which there is no early endocrinological manifestation of the disease, and anatomical prerequisites revealed in our study - a greater frequency of anterior or posterior position of the chiasm, leading to delayed onset or mild severity of visual disturbances.

We identified a statistically significantly higher frequency of null-cell PAs (18.9% in our series versus 0.6% according to the literature) in the study group ($p<0.001$).

With the development of endoscopic endonasal neurosurgery, the possibility of a more radical and safe removal of GPA appeared, in particular, with its extension into the VS. Such surgical treatment is technically not available for transsphenoidal microsurgery or purely sellar endoscopy without the use of extended approaches and angled optics, that is, the results of our study can be compared only with transcranial surgeries of previous years. We established no contraindications to surgical treatment, whereas the contraindication rate was 28% in previous studies.

On the other hand, the analysis of our surgical series showed that, despite a significant increase in the complexity of endoscopic interventions and a high risk of postoperative cerebrospinal fluid leak in the opening of the VS, it is possible to consider endonasal surgeries as the method of choice for the majority of GPAs.

The proposed new classification approach to the group of GPA makes it possible to distinguish groups with relatively low and high risk of high-flow cerebrospinal fluid leak, which, according to our study, correlates with risks of postoperative complications and mortality. Additionally, we emphasize a distinct, albeit the smallest, group of GPAs with extension into the third ventricle (type 3). Such cases require special attention and the decision to have ventriculoperitoneal shunting before or immediately after removal of the tumor.

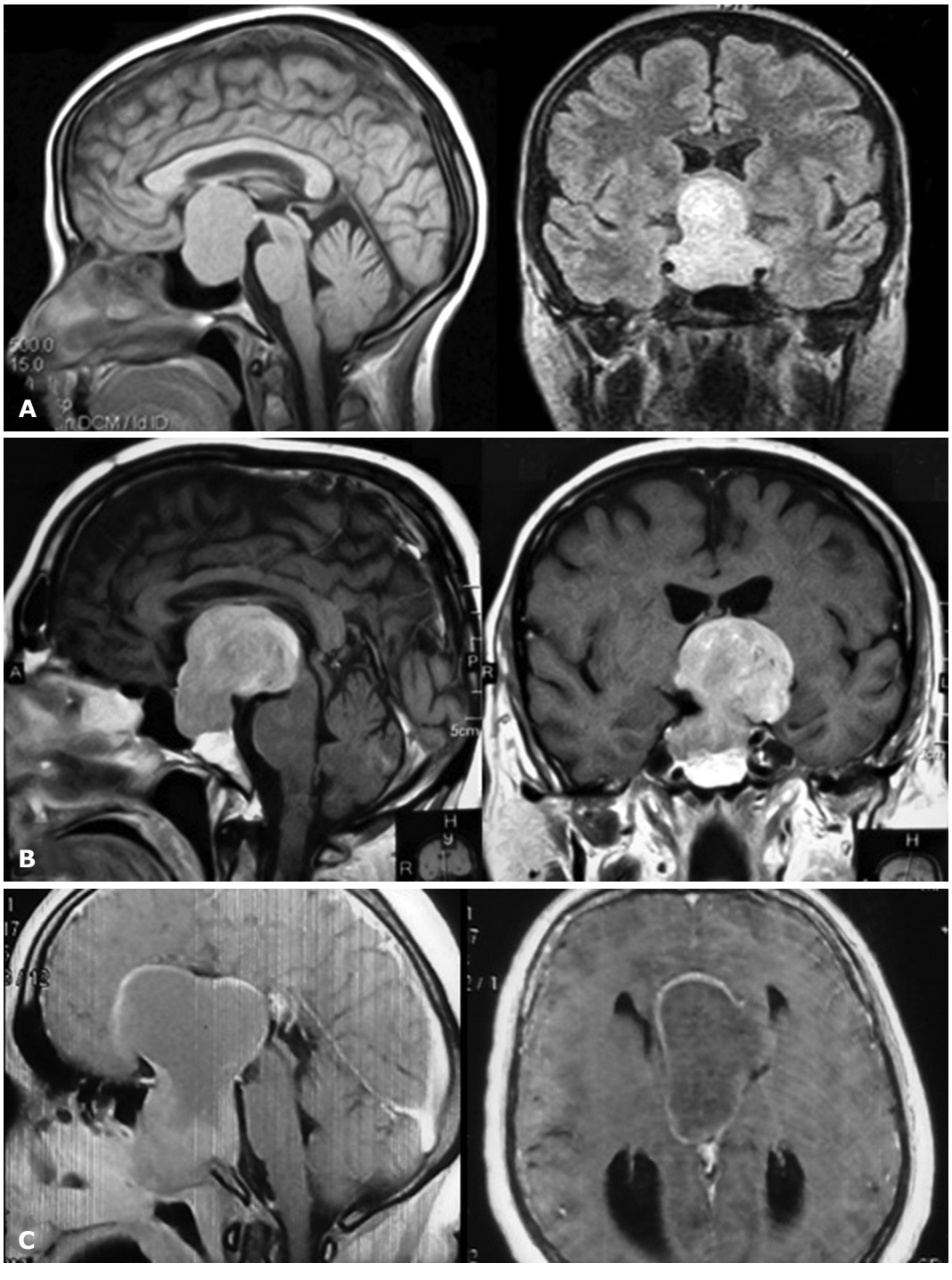

Fig. 7. MR imaging (T1) of the types of extension of giant pituitary adenoma into the ventricular system: A – type 1; B – type 2; C – type 3

Disclosure

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

All procedures performed on patients comply with the ethical standards of institutional and national ethics committees, the 1964 Declaration of Helsinki and its amendments or similar ethical standards.

Informed consent

Informed consent was obtained from each of the patients.

Funding

The study was conducted without sponsorship.

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