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COMPLICATIONS AFTER ENDOSCOPIC ENDONASAL TRANSPHENOIDAL REMOVAL OF PITUITARY ADENOMAS

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The use of endoscopic techniques has significantly expanded the indications for operations performed via transsphenoidal access. Currently, more than 90% of pituitary adenomas are operated transsphenoidally. Transnasal removal of giant pituitary adenomas has become possible. The frequency and structure of postoperative complications have changed due to the transition to endoscopic endonasal access in the removal of pituitary adenomas. An analysis of possible complications after endoscopic endonasal transsphenoidal removal of pituitary adenomas has been conducted. These include complications of the access itself (nosebleeds, nasal septum perforation, olfactory dysfunction, atrophic rhinitis, synechiae, mucoperiosteal flap necrosis, external nasal deformities), infectious complications (meningitis, intracranial abscesses), cerebrovascular accidents (subarachnoid hemorrhage, cerebral vasospasm, injury to large vessels, intracranial hematomas), neuro-ophthalmological complications (visual and oculomotor disorders), endocrine (hypopituitarism, diabetes insipidus, hyponatremia), somatic complications and nasal cerebrospinal fluid rhinorrhea. In conclusion, it should be noted that despite the constant improvement of the endonasal endoscopic removal technique for pituitary adenomas, there remains a risk of quite serious complications, the development of methods for their prevention is still relevant today.

Key words: endoscopic neurosurgery, transsphenoidal neurosurgery, pituitary adenoma

Transnasal operations for pituitary adenomas have been actively used since the 1960s [1, 2]. However, at that time they were performed only using the microsurgical method. Since the mid-1990s, endoscopic techniques have been used in transsphenoidal operations. The use of an endoscope allows for a wide view of the intervention area in good lighting conditions. This makes it possible to remove a tumor from hard-to-reach places under direct visual control, which increases the radicality of the operation and reduces the risk of damaging important anatomical structures [3]. The use of endoscopic techniques has expanded the indications for operations performed via the transsphenoidal approach. Currently, more than 90% of patients with pituitary adenomas undergo transsphenoidal surgery [4-6]. Transnasal removal of tumors that were previously operated on only transcranially has become possible. Elderly and somatically burdened patients are increasingly being operated transnasally. All this has led to the fact that the frequency and

structure of postoperative complications have changed during transsphenoidal removal of pituitary adenomas [3]. Such complications include access complications (nosebleeds, perforation of the nasal septum, olfactory dysfunction, atrophic rhinitis, synechiae, mucoperiosteal flap necrosis, external deformations of the nose), infectious complications (meningitis, intracranial abscesses), cerebrovascular accidents (subarachnoid hemorrhage, cerebral vasospasm, injury to large vessels, intracranial hematomas), neuro-ophthalmological complications (visual and oculomotor disorders), endocrine complications (hypopituitarism, diabetes insipidus, hyponatremia), somatic complications and nasal cerebrospinal fluid rhinorrhea. Complications of access Postoperative nosebleeds Nosebleed is a serious complication after transsphenoidal removal of pituitary adenomas and occurs in 0.7-7.1% of cases [6-11] (Table 1). Most often it develops from the sphenopalatine artery [7]. Nosebleeds can be so intense that extremely invasive procedures are required to stop them, in particular, cases of ligation of the external carotid artery in the neck have been described [7]. To stop nosebleeds, it is recommended to perform endoscopic revision of the nasal cavity with coagulation of its sources. Nasal tamponade should be considered only as a temporary procedure that allows transporting the patient to a specialized hospital [7]. Some studies describe the use of selective embolization of the branches of the maxillary artery as a last resort [10]. The use of a mucoperiosteal flap and the use of antithrombotic drugs are not statistically significant risk factors for the development of postoperative nosebleeds [7]. To reduce the risk of postoperative nosebleeds, it is recommended to avoid damage and prophylactically coagulate the sphenopalatine artery during access in case of its exposure. It is also necessary to pay special attention to blood pressure monitoring in the postoperative period [7]. Atrophic rhinitis The main causes of postoperative atrophic rhinitis are considered to be massive damage to the mucosa during access, as well as intra- and postoperative nosebleeds, which require more active coagulation of the mucous membrane and intranasal vessels. In addition, prolonged postoperative tamponade of the nasal cavity can cause postoperative mucosal atrophy [12]. The incidence of atrophic rhinitis is 1.6% [12]. Olfactory dysfunction Hypoosmia or anosmia occurs in 1.4-12% of cases [8, 9, 12-15]. This complication occurs when the mucous membrane of the olfactory region (the walls of the superior nasal passage; superior turbinates and the upper part of the nasal septum) of the nasal cavity is damaged. The risk of olfactory dysfunction after using a mucoperiosteal flap increases to 26%. In the first month after surgery, this may be due to a large number of crusts in the nasal cavity [16]. Synechiae After endoscopic endonasal approaches, they occur in 8.8-21.4% of cases and lead to nasal breathing disorders [11, 17]. The exposed cartilage of the nasal septum is a source of synechiae in the postoperative period. Usually, new mucous membrane on the septum is formed after 10-14 weeks [18]. The frequency of synechiae formation increases to 20% after using a mucoperiosteal flap [16]. Perforation of the nasal septum In 2.3–3.7% of cases, endoscopic skull base surgery is complicated by perforation of the nasal septum [12–17]. When using a mucoperiosteal flap, this occurs

almost 4 times more often (14.4%) [18]. This complication can manifest itself as headache, dryness and nasal congestion. Septoplasty is often required to restore adequate nasal breathing [12].

Necrosis of the mucoperiosteal flap

Necrosis of the mucoperiosteal flap occurs due to disruption of its blood supply and occurs in 1.3% of cases [18]. This condition is primarily dangerous due to infectious complications. Thus, in the study by D. Joseph et al., all 8 patients with flap necrosis developed meningitis. Epidural empyema was also detected in 4 of them. The use of elastic tampons and balloon catheters for tamponade of the nasal cavity does not increase the risk of flap necrosis. The only statistically significant factor in flap necrosis was the use of adipose tissue for plastic surgery of the postoperative skull base defect. However, the reasons for such a dependence have not been described [18]. External deformities of the nose Deformation of the nasal dorsum can appear only after the use of the mucoperiosteal flap (in 5.8% of cases) [19]. The simultaneous use of an extended transsphenoidal approach and a mucoperiosteal flap increases the risk of external deformities. The reason for this is probably the use of large flaps, due to which the wound surface of the nasal septum increases [19]. There are suggestions that ischemia after flap cutting in combination with work through both nasal passages can lead to the destruction of the nasal dorsum framework (lateral cartilages and nasal septum) and cause its deformation [19]. One of the reasons for the deformation of the nasal dorsum is an excessively high collection of plastic material in the form of bone and cartilage structures. Nasal liquorrhea With the development of endoscopic endonasal surgery, extended transnasal approaches began to be widely used. The area from the olfactory fossa to the craniocervical junction, i.e. almost the entire bony base of the skull, became accessible for surgical manipulations [20]. The formed defect of the base of the skull can have a large area, which significantly increases the risk of developing nasal liquorrhea, which is fraught with dangerous consequences in the form of meningitis [20]. The incidence of nasal cerebrospinal fluid leakage after pituitary adenoma removal is 0.6–16.7% (Table 2) [13, 21]. Preoperative factors that increase the risk of postoperative cerebrospinal fluid leakage include underweight or overweight. Normally, the body mass index is 18.5–24.99 and is calculated using the formula $I = m : h^2$, where m is body weight in kilograms and h is height in meters [22]. Also, the absence of a tumor capsule, the presence of defects in it, and significant defects in the bones of the skull base are considered to be high-risk factors for postoperative cerebrospinal fluid leakage [20]. Currently, layered plastic surgery of the postoperative skull base defect with various allo- and autotissues has entered everyday practice, which has significantly reduced the incidence of cerebrospinal fluid leakage [20]. It is worth noting that the use of blood-supplied flaps for plastic surgery of the skull base

defect statistically significantly reduces the risk of postoperative nasal cerebrospinal fluid leakage [22]. Infectious complications Patients with pituitary adenomas have an increased risk of infectious complications in the postoperative period. This is primarily due to dysfunction of the hypothalamus, which is the central link in the nervous regulation of homeostasis, including immune homeostasis. There is a large amount of both experimental data and clinical observations showing the presence of immunodeficiency in case of damage to the hypothalamic structures. In particular, a decrease in the immune response, including secondary, to microbial and non-microbial antigens has been found [23]. The risk of infectious complications is also associated with the technique of transsphenoidal operations itself. When intraoperative cerebrospinal fluid leakage occurs, a direct connection is created between the bacterially contaminated nasal cavity and the sterile cranial cavity, which can lead to the penetration of pathogens intracranially.

Meningitis

Meningitis is the most common infectious complication after transsphenoidal removal of pituitary adenomas. It usually manifests itself as febrile fever and meningeal signs. Nonspecific signs of inflammation appear in the blood test, and an increase in cytosis, lactate, protein, and glucose consumption in the cerebrospinal fluid. The main causative agents of postoperative meningitis are Streptococcus pneumoniae, Staphylococcus epidermidis, Haemophilus influenzae, Corynebacterium spp., Streptococcus viridans, Serratia spp., Enterococcus spp., Klebsiella pneumoniae, Stenotrophomonas maltophilia, Acinetobacter baumannii, Candida albicans [24]. The causes of postoperative meningitis are different, but are mainly associated with violation of aseptic and antiseptic rules. Of these, the most important are the nature of the sanitary treatment of the operating room, the duration of the operations, their technique, the contingent and the number of people present at the operation [1]. A high risk of meningitis is associated with intra- and postoperative cerebrospinal fluid leakage, an operation lasting more than 60 minutes, external lumbar drainage and repeated operations aimed at sealing the cranial cavity [15]. On average, meningitis manifests itself within 14 days after the operation [24]. Despite the need to pass neurosurgical instruments through a narrow, conventionally contaminated corridor of the nasal cavity during transnasal operations, the incidence of meningitis after such operations, according to some authors [15, 25], is no higher than after transcranial ones and is 0.6-7.1% (on average 2%). Intracranial abscesses One of the most dangerous and potentially fatal complications after endoscopic surgery of pituitary adenomas is an intracranial abscess. According to the literature [26], the incidence of such abscesses is 0.2-0.6%. The most common etiologic cause of intracranial abscess are staphylococci and streptococci, found in 30% of cases. In some cases, Neisseria, Micrococcus, Citrobacter, Escherichia coli, Brucella, Salmonella, Corynebacterium and Mycobacterium are cultured. Due to the lack of specific clinical symptoms and radiographic signs, establishing a correct diagnosis is difficult. Often, an intracranial abscess that occurs after transsphenoidal

removal of a pituitary adenoma becomes an intraoperative finding. Some authors [27] consider transsphenoidal drainage to be the method of choice for treating pituitary abscesses that occur after transnasal removal of pituitary adenomas. Transsphenoidal access allows avoiding intracranial spread of infection. During the operation, the key points are the removal of pus and wide trepanation of the anterior wall of the sinus and the bottom of the sella turcica to ensure aeration and drainage of the abscess cavity [27]. Cases of transcranial removal of pituitary abscesses have also been described. The course of the postoperative period after such operations is more severe than after transnasal ones, the incidence of meningitis is higher [27]. Impaired cerebral circulation Damage to large arteries Damage to large vessels of the circle of Willis is one of the most formidable complications during removal of pituitary adenomas [1]. A high-risk factor for vascular damage is the variability of the anatomy of the intracavernous segment of the internal carotid artery (ICA), which can shift significantly in patients with pituitary adenomas [28]. In acromegaly and Itsenko-Cushing's disease, the arterial walls become more fragile due to arterial hypertension and atherosclerotic changes, and the anatomy of the nasal cavity, sphenoid sinus, and sella turcica changes, which complicates the surgeon's orientation in the surgical wound and increases the risk of injury to arterial vessels [28]. In the work of A. Romero et al. [28], materials on 7336 patients from the reviewed literature and 800 patients of their own sample who underwent endonasal endoscopic removal of a skull base tumor were analyzed. Damage to large intracranial arteries occurred in 29 (0.36%) cases. The most common primary pathology in patients who suffered arterial injury was pituitary adenoma - 13 cases, of which 11 cases were represented by damage to the ICA and one case each - to the anterior communicating and ophthalmic arteries [28]. The consequences of vascular injury vary in severity up to and including death. Trauma to the vessel may result in intracranial hematoma, carotid occlusion, stenosis, pseudoaneurysm formation, carotid-cavernous ostium, subarachnoid hemorrhage, vasospasm, or distal embolism with cerebral ischemia [28]. Occlusion or stenosis of the carotid arteries may occur secondary to prolonged tamponade during arterial bleeding cessation [28]. The main cause of ICA injury is incorrect surgeon orientation in the surgical wound or excessively aggressive actions in the cavernous sinus. The incidence of ICA injury is inversely proportional to the surgeon's experience [29]. Subarachnoid hemorrhage Subarachnoid hemorrhage (SAH) is a rare complication after transsphenoidal surgery of pituitary adenomas and accounts for 0.09-3.6% (Table 3) [11, 13]. The most likely cause of SAH is bleeding from the unremoved suprasellar component of the tumor and the anterior vessels of the circle of Willis. The risk of postoperative SAH is higher after removal of giant tumors and in the presence of a large suprasellar part of the tumor [15]. Cerebral vasospasm Isolated cases of symptomatic vasospasm after transsphenoidal surgeries have been described in the world literature. Its pathophysiology after transsphenoidal surgeries is not yet fully understood. The most likely cause is intraoperative arterial trauma and subarachnoid hemorrhage. Meningitis can be another cause. Vasospasm often leads to ischemic changes in the brain

and requires intensive care [30]. The work of A. Puri et al. [31] included 9 cases of symptomatic vasospasm described in the world literature since 1980. Of the 9 cases, only 2 ended in recovery, 3 cases - in disability (patients were discharged with hemiparesis, unilateral amaurosis and aphasia) and 4 - in death. A risk factor for the development of vasospasm is presumably the large size of the tumor [31]. Intracranial hematomas A dangerous complication after removal of pituitary adenomas are intracranial hematomas (0.68-3.7%) [6, 21]. They can lead to visual impairment and severe neurological deficit due to compression of the cranial nerves and surrounding nerve structures. N. Sudhakar et al. [32] describe their own experience of transsphenoidal surgery, the frequency of intracranial hematomas after which was 0.8%. According to the literature review performed by E. Laws [33], the frequency of such hematomas reaches 3%. In the article by T. Origitano et al. [34], neurological deficit due to postoperative hematomas or compression of nerve structures by components of plastic surgery of the postoperative skull base defect was 7.4% of cases. F. Wang et al. [13] describe 8 (0.69%) cases out of 1166, when hematomas formed in the bed of the removed tumor, 7 of them required endoscopic endonasal removal due to the resulting visual impairment. Only in 3 of 7 patients, vision was restored to its previous level. Some authors [35] observed the occurrence of subdural hematomas after endoscopic transsphenoidal surgery. In the works describing complications after endoscopic skull base surgery, there is no separate detailed description of intra- and extracapsular hematomas, hemorrhages in the unremoved part of the tumor. Neuro-ophthalmological complications Visual impairment The main causes of visual impairment after transsphenoidal operations are intraoperative trauma to the optic nerve, its ischemia or compression of the visual pathways by a hematoma or fragments of skull base plastic surgery. In the world literature [13, 15], the topic of visual impairment is extremely poorly represented. Basically, information is reduced to indicating the frequency of visual impairment: deterioration of visual function after transsphenoidal adenomectomy occurs in 0.43-2.4% of cases. Oculomotor impairment Postoperative dysfunction of the oculomotor nerves (III, IV, VI) is most often observed in adenomas growing into the cavernous sinus [23]. Their cause, as well as visual ones, is considered to be intraoperative damage to the nerves and hematoma in the bed of the removed tumor [36]. G. Frank et al. [36] consider the VI nerve to be the most vulnerable due to its free location in the cavernous sinus. In turn, M. Koutourousiou et al. [21] describe the most frequent lesion of the oculomotor nerve. When using the endoscopic endonasal approach, oculomotor complications occur in 0.68-11.1% of cases [6, 21].

Endocrine complications

Hypopituitarism

Hypopituitarism is a disease manifested by complete or partial loss of secretion of pituitary tropic hormones and, as a consequence, insufficiency of the corresponding organs

of the peripheral endocrine system [23]. Anterior pituitary insufficiency after removal of pituitary adenomas is a consequence of intraoperative trauma to the adenohypophysis and is called secondary [23]. Most often, postoperative hypopituitarism is transient (up to 16.7% of cases) (Table 4), less often it becomes permanent.

In macroadenomas, the pituitary gland in the sella turcica is significantly compressed and difficult to discern intraoperatively, which can lead to its damage during tumor removal and, as a consequence, to hypopituitarism [13]. According to a number of authors [8, 13], hypopituitarism occurs due to active work with an aspirator and electrocoagulation in the sella turcica. Therefore, they recommend, if possible, replacing electrocoagulation with chemical hemostatic agents during tumor removal (Surgicel, etc.) [8, 13]. Diabetes insipidus Diabetes insipidus is a syndrome manifested by severe thirst and the excretion of a large amount of dilute urine [23]. In neurosurgical patients, its main cause is a deficiency or impaired secretion of antidiuretic hormone. This may occur as a result of compression of the hypothalamus, pituitary stalk, or neurohypophysis by a tumor or during surgical manipulations in the chiasmatic-sellar region (CSR). Less often, diabetes insipidus is caused by an inflammatory process (meningitis, encephalitis). Thus, transient diabetes insipidus is observed in an average of 30% of patients after removal of pituitary adenomas. However, in 3-5% of cases of operated pituitary adenomas, the transient form becomes permanent [37]. Risk factors for diabetes insipidus are similar to risk factors for hypopituitarism [8].

Hyponatremia

Hyponatremia is one of the most serious homeostasis disorders in patients with pituitary adenomas, requiring close attention. This condition is characterized by a decrease in the sodium level in the blood serum to less than 135 mmol/l. In the absence of timely diagnosis and adequate therapy, hyponatremia can lead to serious complications. Thus, according to K. Asadollahi et al. [38], in hospitalized patients with various pathologies with a sodium level of 120-125 mmol/l, mortality reaches 23%, and less than 115 mmol/l - 50%. According to the meta-analysis of D. Cote et al. [39], the incidence of hyponatremia after transsphenoidal surgery is 4-12%. The main cause of hyponatremia after removal of pituitary tumors is mainly the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) [40]. However, a number of authors consider cerebral salt-wasting syndrome to be the leading cause of postoperative hyponatremia [40]. The presence of uncompensated hypopituitarism before surgery increases the incidence of hyponatremia after surgery [40]. In patients receiving glucocorticoid hormones in the perioperative period, the possibility of acute adrenal insufficiency as a cause of hyponatremia is excluded. The main factor in the uncontrolled release of antidiuretic hormone is mechanical damage to the neurohypophysis or pituitary stalk [40].

Somatic complications

The main cause of organ complications after removal of pituitary adenomas is damage to diencephalic structures. Cardiovascular, respiratory, renal, hepatic dysfunction, gastrointestinal paresis and thrombocytopenia may develop. Despite the obvious leading role of diencephalic structures in regulating the function of vital organs, very few studies have been devoted to the problem of organ dysfunction development in case of damage to the diencephalon [41]. Cardiovascular dysfunction in patients with CSR tumors (including pituitary adenomas) and complicated postoperative period is manifested primarily by arterial hypotension. Other life-threatening disorders of systemic hemodynamics are not typical for this category of patients. The causes of arterial hypotension, which develops in more than 2/3 of patients with pituitary tumors with a complicated postoperative period, may be adrenal insufficiency, thyroid insufficiency, panhypopituitarism, hypovolemia during decompensation of diabetes insipidus, and direct damage to the diencephalic structures [41]. Respiratory dysfunction in patients with pituitary adenomas and a complicated early postoperative period develops as often as arterial hypotension, in more than 2/3 of cases [41]. Intestinal dysfunction, defined as gastrointestinal tract paresis, is detected in 70% of patients with pituitary tumors and a complicated early postoperative period. Sepsis and damage to the diencephalic structures were found to be reliable causes of intestinal dysfunction [41]. Thrombocytopenia, renal and hepatic dysfunction develop significantly less frequently - in 28.4 and 1% of observations, respectively [41].

The most common isolated infection complicating the postoperative period is pneumonia, and the most common combined infection is meningitis and pneumonia, as well as pneumonia and urinary tract infection [41]. In the foreign literature, a similar frequency of systemic complications is mainly described. An exception is the study of R. Fahlbusch et al. [42], where in 4% of cases after surgery, deep vein thrombosis of the lower extremities developed with subsequent development of pulmonary embolism. Two percent of patients died due to postoperative pneumonia. The authors of articles on complications after transsphenoidal surgery agree that systemic complications occur significantly more often in the older age group (6.7-32%) [43]. In the work of S. Hentschel et al. [44], it was noted that somatic complications developed in 32% of patients over 70 years of age.

Postoperative mortality

The fatality rate after transsphenoidal adenomectomy is low and amounts to 0–3.2% [8]. There are several reviews of fatal outcomes after transsphenoidal surgery of pituitary adenomas in the world literature [8, 45, 46]. The study by H. Halvorsen et al. [45] included 506 transsphenoidal adenomectomies (268 performed microsurgically and 238 endoscopically). The fatality rate in this series was 0.6%. The causes of fatal outcomes were pulmonary embolism and massive cerebral edema in a patient with pituitary adenoma apoplexy. In the work by J. Gondim et al. [25] in a series of 301 endoscopic adenomectomies, the fatality rate was 1%. In all cases, the cause of fatal outcome was

heart failure, which occurred no earlier than 2 weeks after surgery. The meta-analysis by A. Tabaee et al. [46] included 824 patients after endoscopic adenomectomy. There were 2 fatal outcomes in this study (0.24%). In both cases, the cause of death was intraoperative trauma to large vessels. The works of B.A. Kadashev et al. [23, 47] describe surgical treatment of large and giant pituitary adenomas, in which the mortality rate was fundamentally different from that for smaller adenomas. Previously, with different types of operations (transcranial and transnasal microscopic), it was 18%. The main cause of fatal outcomes was hemorrhage into the unremoved part of a large tumor. Currently, mortality is significantly lower with endoscopic operations. Thus, E. Constantino et al. [11] report mortality after removal of giant adenomas in 7.1% of cases. The causes of death in this study were massive intraventricular hemorrhage and metabolic disturbances due to diabetes insipidus [11]. However, there are studies [21] describing the removal of giant pituitary adenomas without fatal outcomes.

Conclusion

Despite the constant improvement of the technique of transnasal removal of pituitary adenomas, there is a risk of complications, including potentially fatal ones. Thus, the development of effective methods for preventing complications after endoscopic endonasal removal of pituitary adenomas is still relevant today.

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