

## Клинические синдромы сдавленного и хирургически пересеченного стебля гипофиза

© Л.И. Астафьева\*, Б.А. Кадашев, П.Л. Калинин, М.А. Кутин, И.С. Клочкова, Д.В. Фомичев, О.И. Шарипов, Д.Н. Андреев

ФГАУ «Национальный медицинский исследовательский центр нейрохирургии им. акад. Н.Н. Бурденко» Минздрава России, Москва, Россия

**Обоснование.** Стебель (ножка) гипофиза (СГ) — анатомическое образование, состоящее из системы порталных сосудов и аксонов ядер гипоталамуса, заканчивающихся в задней доли гипофиза. Известно, что хирургическое повреждение или сдавление СГ опухолью или другим объемным процессом может приводить к гипопитуитаризму, несахарному диабету, гиперпролактинемии. Однако в литературе практически нет исследований о степени этих нарушений в зависимости от повреждения или компрессии СГ в клинической практике.

**Цель исследования** — изучение до- и послеоперационных эндокринных нарушений у больных с опухолями хиазмально-селлярной области (ХСО) со сдавленным и сохраненным или вынужденно пересеченным во время нейрохирургической операции СГ.

**Материал и методы.** У 82 пациентов сдавленный до операции СГ был сохранен (41 больной с гормонально-неактивной аденомой эндосупраселлярной локализации и 41 больной с супраселлярной менингиомой), а у 57 пациентов во время транскраниальной операции СГ был пересечен (46 больных со стебельной краниофарингиомой, 11 — с гормонально-неактивной эндосупраселлярной аденомой гипофиза). До и через 6 мес после операции у всех больных определяли уровень пролактина (ПРЛ), ТТГ, ЛГ, ФСГ, св.Т4, кортизола, тестостерона или эстрадиола.

**Результаты.** У 37,4% пациентов с опухолями ХСО, сдавливающими СГ, выявлена гиперпролактинемия. Устранение сдавления СГ приводило к нормализации уровня ПРЛ у большинства больных и не сопровождалось нарастанием симптомов гипопитуитаризма. При пересечении СГ у 100% пациентов развился пангипопитуитаризм, у 93% — несахарный диабет. При этом у 58,7% больных с краниофарингиомами и 81,9% с гормонально-неактивными аденомами гипофиза не отмечено появления гиперпролактинемии.

**Заключение.** Учитывая различие в симптоматике, мы выделили два синдрома — синдром сдавления СГ и синдром пересечения СГ. Синдром сдавления СГ опухолью ХСО характеризовался преимущественно гиперпролактинемией (37,4% случаев); устранение сдавления СГ при удалении опухоли приводило к нормализации уровня ПРЛ у большинства больных и не сопровождалось нарастанием симптомов гипопитуитаризма. Синдром хирургического пересечения СГ у пациентов с краниофарингиомой (КФ) и неактивной аденомой гипофиза (НАГ) проявлялся пангипопитуитаризмом у всех больных и постоянной формой несахарного диабета у большинства из них. Причины отсутствия гиперпролактинемии у многих пациентов с пересечением СГ требуют изучения. Нельзя исключить как ишемию аденогипофиза (в результате нарушения его кровоснабжения) с частичной или полной атрофией лактотрофных клеток, так и ревакуляризацию гипофиза с восстановлением транспорта дофамина.

*Ключевые слова:* пролактин, стебель (ножка) гипофиза, компрессия стебля гипофиза, хирургическое пересечение стебля гипофиза, несахарный диабет.

## Clinical syndromes of compression and surgical transection of the pituitary stalk

© Liudmila I. Astafyeva\*, Boris A. Kadashev, Pavel L. Kalinin, Maxim A. Kutin, Irina S. Klochkova, Dmitry V. Fomichev, Oleg I. Sharipov, Dmitry N. Andreev

Burdenko Neurosurgical Institute, Moscow, Russia

**Background.** The pituitary stalk (PS) is an anatomical structure consisting of the portal vessel system and axons of the hypothalamic nuclei terminating in the posterior pituitary lobe. Surgical injury or compression (by a tumor or another space-occupying process) of the PS can lead to hypopituitarism, diabetes insipidus, and hyperprolactinemia. However, the literature lacks studies on the extent of these disorders depending on PS injury or compression in clinical practice.

**Aim.** The study aim was to investigate pre- and postoperative endocrine disorders in patients with chiasmo-sellar region (CSR) tumors and the PS compressed and preserved or involuntarily transected during neurosurgery.

**Material and methods.** The PS compressed before surgery was preserved in 82 patients (41 patients with non-functioning endosuprasellar adenoma and 41 — with suprasellar meningioma). The PS was transected during transcranial surgery in 57 patients (46 patients with pituitary stalk craniopharyngioma and 11 patients with non-functioning endosuprasellar pituitary adenoma). All patients underwent blood tests for prolactin (PRL), TSH, LH, FSH, free T4, cortisol, testosterone, or estradiol levels before and 6 months after surgery.

**Results.** Hyperprolactinemia was detected in 37.4% of patients with CSR tumors compressing the PS. Elimination of PS compression led to normalization of the PRL level in most patients and was not accompanied by worsening of hypopituitarism symptoms. Transection of the PS resulted in panhypopituitarism in 100% of patients and diabetes insipidus in 93% of cases. There was no evidence of hyperprolactinemia in 58.7% of patients with craniopharyngiomas and 81.9% of patients with non-functioning pituitary adenomas.

**Conclusion.** Given the difference in symptoms, we distinguished two syndromes: PS compression syndrome and PS transection syndrome. Syndrome of PS compression by a CSR tumor was characterized mainly by hyperprolactinemia (37.4% of cases); elimination of PS compression due to tumor resection led to normalization of the PRL level in most patients and was not accompanied by worsening of hypopituitarism symptoms. Syndrome of surgical PS transection in patients with craniopharyngioma (CP) and non-functioning pituitary adenoma (NFPA) manifested as panhypopituitarism in all patients and as permanent diabetes insipidus in most of them. The causes for the absence of hyperprolactinemia in many patients with the transected PS require further re-

search. We can not exclude both adeno-hypophysis ischemia (due to its impaired blood supply) with partial or complete atrophy of lactotrophic cells and pituitary revascularization with restoration of dopamine transport.

*Keywords:* prolactin, pituitary stalk, pituitary stalk compression, surgical transection of pituitary stalk, diabetes insipidus.

## ABBREVIATIONS

PS – pituitary stalk  
CP – craniopharyngioma  
NFPA – non-functioning pituitary adenoma  
DI – diabetes insipidus  
PRL – prolactin  
GH – growth hormone  
LH – luteinizing hormone  
FSH – follicle-stimulating hormone  
FT4 – free thyroxine  
ACTH – adrenocorticotropic hormone  
ADH – antidiuretic hormone  
CSR – chiasm-sellar region  
PSIS – pituitary stalk interruption syndrome

## INTRODUCTION

The term “the pituitary stalk interruption syndrome” used in literature can refer to several different conditions: pituitary stalk (PS) compression with a suprasellar tumor (pituitary macroadenoma, meningioma, craniopharyngioma, or any other space-occupying process); neurosurgical transection of the pituitary stalk; pituitary stalk rupture as a result of neurotrauma; and pituitary stalk agenesis during embryogenesis (a congenital syndrome).

The clinical presentation involves hyperprolactinemia, diabetes insipidus (DI), and deficiency of pituitary tropic hormones because of disturbed hypothalamic control (hypogonadism, hypothyroidism, hypocorticism, and growth hormone deficiency).

Although the same term is used for all these conditions, their pathogenesis, clinical symptoms, and prognosis differ significantly. We have conducted a comparative study of endocrine disorders in patients with pituitary stalk compression by a tumor or neurosurgical pituitary stalk transection.

## OBJECTIVE

This study was aimed at investigating pre- and postoperative endocrine disorders in patients with tumors in the chiasm-sellar region (CSR), with the pituitary stalk compressed and preserved or deliberately transected during neurosurgery.

## METHODS

### Study design

The study involved 139 patients with tumors in the chiasm-sellar region, who had undergone tumor resection, with pituitary stalk either transected or preserved, at the

N.N. Burdenko National Research and Practical Center for Neurosurgery during the period between 2000 and 2016.

PRL, TSH, LH, FSH, FT4, cortisol, testosterone or estradiol levels were measured prior to surgery and 6 months after it.

### Inclusion criteria

Age >18 years

Tumor in the chiasm-sellar region causing pituitary stalk compression (pituitary adenoma, craniopharyngioma, or meningioma)

The patient underwent neurosurgical resection of tumor in the chiasm-sellar region, with the pituitary stalk either transected or preserved.

### Study center

The study was carried out at the N.N. Burdenko National Research and Practical Center for Neurosurgery, Ministry of Healthcare of the Russian Federation (Department of Skull Base Tumors specializing in surgical treatment of tumors in the chiasm-sellar region).

### Study duration

The patients were examined preoperatively and 6 months after neurosurgical treatment.

### Medical intervention

The neurosurgeries were performed through the transcranial microsurgical or endoscopic transsphenoidal approaches.

Upon transcranial resection of a pituitary stalk craniopharyngioma or endosuprasellar pituitary adenoma, the pituitary stalk was transected in order to perform radical resection of the suprasellar portion of the capsule infiltrated by the tumor.

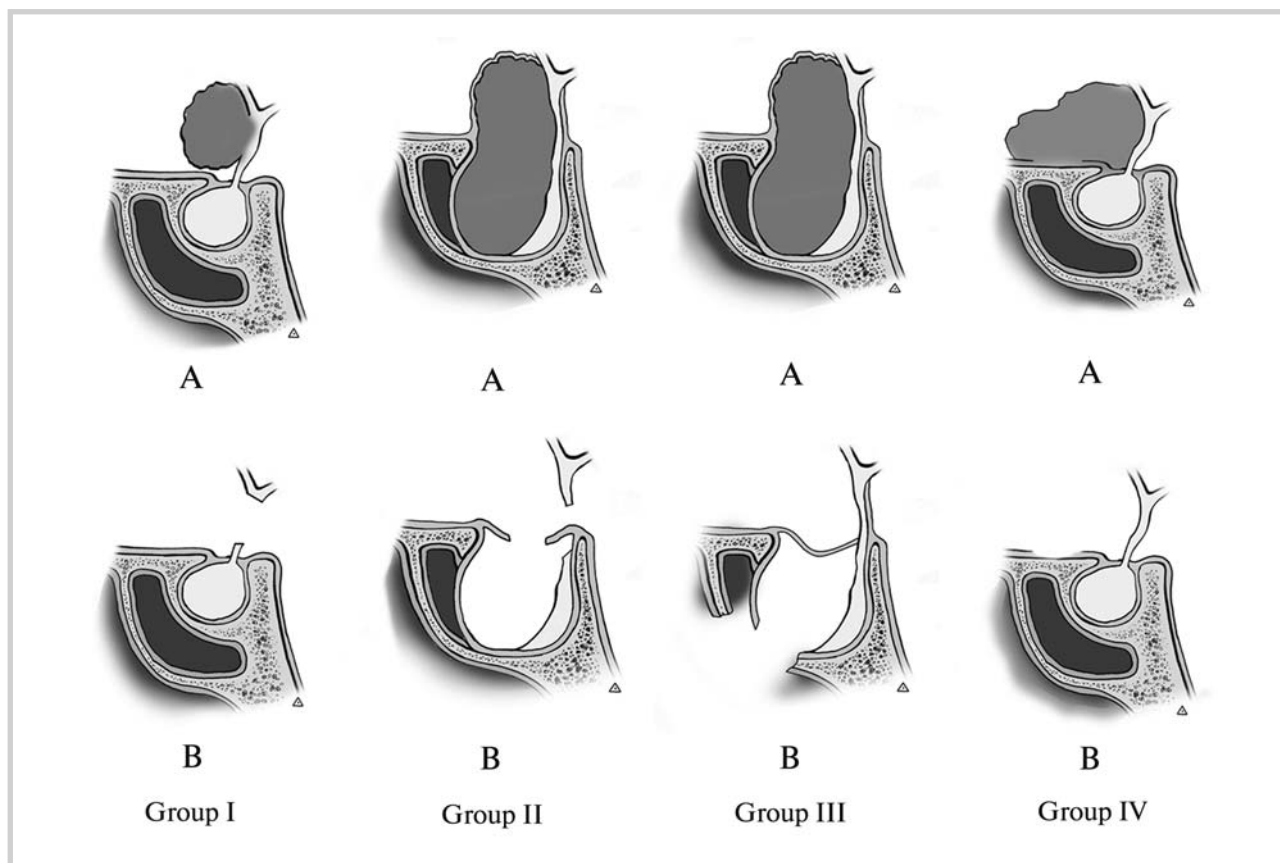
Upon the endoscopic transsphenoidal approach, intracapsular resection of pituitary adenomas without pituitary stalk transection was carried out.

Transcranial microsurgical resection of suprasellar meningiomas was conducted without pituitary stalk transection

The patients with secondary postoperative hypocorticism, hypothyroidism, and hypogonadism were treated with glucocorticoids, thyroid hormones, and sex hormones, respectively. Patients with diabetes insipidus were treated with desmopressin. Cabergoline therapy was used to correct hyperprolactinemia.

### Primary outcome of the study

The function of the pituitary gland was assessed according to the results of hormone blood test and parameters of water-electrolyte metabolism.



**Fig. 1. Tumors in the chiasm-sellar region before (A) and after (B) surgical treatment (scheme).**

**Group I:** A – pituitary stalk craniopharyngioma with the damaged pituitary stalk and preserved pituitary gland before the surgery.

**B** – the condition after transcranial resection of pituitary stalk craniopharyngioma involving pituitary stalk transection; the pituitary gland is preserved.

**Group II:** A – endosuprasellar pituitary adenoma with compressed pituitary gland and pituitary stalk before the surgery.

**B** – the condition after transcranial resection of endosuprasellar pituitary adenoma involving pituitary stalk transection; the pituitary gland is compressed.

**Group III:** A – endosuprasellar pituitary adenoma with compressed pituitary gland and pituitary stalk before the surgery.

**B** – the condition after intracapsular transnasal endoscopic resection of the endosuprasellar pituitary adenoma without pituitary stalk transection; the pituitary gland is compressed.

**Group IV:** A – suprasellar meningioma with pituitary stalk compression and preserved pituitary gland before the surgery.

**B** – the condition after transcranial resection of suprasellar meningioma without pituitary stalk transection; the pituitary gland is preserved.

### Subgroup analysis

The patients were subdivided into four groups according to tumor histology and location, as well as depending on whether the pituitary stalk had been intraoperatively transected or preserved (Fig. 1):

· **Group I:** 46 patients with pituitary stalk craniopharyngioma who had undergone transcranial surgery. These tumors had almost completely destroyed the pituitary stalk, which was totally transected during the surgery. In these patients, the pituitary gland remained anatomically preserved both before and after the surgery.

· **Group II:** 11 patients with non-functioning endosuprasellar pituitary adenoma (NFPA) who had undergone transcranial surgery in 2000–2003. These tumors were compressing the pituitary stalk, which was subsequently transected when performing radical resection of the suprasellar portion of the capsule infiltrated by the tumor to reduce the risk of tumor recurrence. The pituitary gland in these patients was anatomically altered both before and after the surgery.

· **Group III:** 41 patients with non-functioning endosuprasellar pituitary adenoma (NFPA) compressing the pituitary gland and its stalk; the tumors were resected intracapsularly through the endoscopic endonasal transsphenoidal approach. The pituitary stalk was preserved, while the pituitary gland was anatomically altered both before and after the surgery.

· **Group IV:** 41 patients with suprasellar meningioma in whom the pituitary stalk compressed before the surgery was preserved. The pituitary gland in these patients remained anatomically preserved before and after the transcranial surgery.

### Outcome measurement techniques

The intraoperative characteristics of the condition of the pituitary gland and the pituitary stalk were evaluated. Moderate hyperprolactinemia was confirmed by the test performed twice. The patient was diagnosed with secondary hypothyroidism if low FT4 level together with the normal or low TSH level was revealed. The diagnosis of

**Table 1. Characteristics of study groups and endocrine disorders revealed in patients before and after surgery**

Parameter	Group I	Group II	Group III	Group IV
	Pituitary stalk craniopharyngioma	NFPA with pituitary stalk transection	NFPA without pituitary stalk transection	Suprasellar meningioma
Compression of the pituitary gland	-	+	+	-
Pituitary stalk compression	+	+	+	+
n	46	11	41	41
Age, min-max (median), years	15–64 (36)	18–57 (45)	32–67 (53)	35–68 (48)
Sex	F 31/M 15	F 7/M 4	F 25/M 16	F 37/M 4
Preoperatively				
PRL level, min-max (median), mU/l	115–3000 (440)	185–1085 (500)	140–1980 (550)	113–4050 (377)
Hyperprolactinemia, n (%)	19 (41.3%)	4 (36.3%)	16 (39.0%)	13 (31.7%)
Hypothyroidism, n (%)	12 (26.0%)	4 (36.3%)	14 (34.1%)	3 (7.3%)
Hypocorticism, n (%)	7 (15.2%)	2 (18.2%)	11 (26.8%)	2 (4.9%)
Hypogonadism, n (%)	38 (82.6%)	8 (72.7%)	33 (80.5%)	4 (9.7%)
Diabetes insipidus, n (%)	11 (23.9%)	-	-	1 (2.4%)
Postoperatively				
Intraoperative pituitary stalk transection	+	+	-	-
Preservation of the pituitary gland*	preserved	?	?	preserved
PRL level, min-max (median), mU/l	35–3600 (380)	33–1080 (335)	13–2–610 (235)	93–740 (280)
Hyperprolactinemia, n (%)	19(41.3%)	2 (18.1%)	1 (2.4%)	2 (4.9%)
Hypothyroidism, n (%)	46(100%)	11 (100%)	12 (29.2%)	3 (7.3%)
Hypocorticism, n (%)	46(100%)	11 (100%)	10 (24.3%)	2 (4.9%)
Hypogonadism, n (%)	46(100%)	11 (100%)	29 (70.7%)	5 (12.1%)
Diabetes insipidus**, n (%)	43 (93.5%)	10 (90.9%)	0	1 (2.4%)

\*In groups II and III, it is unclear whether the pituitary gland was preserved. Furthermore, the pituitary gland could have been additionally damaged intraoperatively.

\*\*Transient diabetes insipidus that had regressed earlier than 6 months after the surgery was not taken into account in analysis of study results.

secondary adrenal insufficiency was made in patients having the morning cortisol level below 120 nmol/l or the cortisol level of 120–350 nmol/l and corresponding clinical symptoms. The diagnosis of secondary hypogonadism was made in women of reproductive age having amenorrhea and in postmenopausal women having low blood level of gonadotropins. Men were diagnosed with secondary hypogonadism if testosterone level was below 8 nmol/l. The PRL level > 550 mU/l in females and > 414 mU/l in males was a criterion indicative of moderate hyperprolactinemia. The diagnosis of diabetes insipidus was made on the basis of hypotonic polyuria (> 40 ml/kg per day) and polydipsia, while the glycemic indicators were normal.

### Statistical analysis

Statistical analysis of the results was performed using Excel and STATISTICA 6.0 for Windows application software packages. Relative values were compared using the  $\chi^2$  test (the differences were considered significant at  $P < 0.05$ ).

## RESULTS

The study groups differed in a combination of pre- and postoperative conditions (the function of the pituitary stalk and the pituitary gland) was either preserved or disturbed). Study results are shown in Table 1.

Resection of craniopharyngiomas involving pituitary stalk transection led to panhypopituitarism in all patients (group I). Forty-three patients developed diabetes insipidus (DI) (only 11 patients had DI before the surgery). All patients needed hormone replacement therapy with glucocorticoids, thyroid hormones, sex hormones, and vasopressin analogues. Three patients did not have DI. Hyperprolactinemia was postoperatively revealed in 19 patients (41.3% of cases). The PRL level became normal in 5 out of 19 patients with the preoperatively elevated values, while in 5 patients with normal preoperative PRL level it became elevated. The maximum PRL level was 3600 mU/l. Two patients developed hypoprolactinemia (35 and 50 mU/l).

The same situation was observed for the patients subjected to resection of non-functioning endosuprasellar adenomas involving pituitary stalk transection (group II). All these 11 patients had either newly developed or aggravated hypopituitarism symptoms. Diabetes insipidus developed in 10 out of 11 patients. Moderate hyperprolactinemia was preoperatively revealed in 4 patients. After the surgery involving pituitary stalk transection, only 2 patients had elevated PRL levels. One patient developed hypoprolactinemia (33 mU/l).

Contrariwise, hypopituitarism symptoms regressed in group III patients who had undergone adenoma resection without pituitary stalk transection: recovery of sexual function, regression of hypothyroidism, and regression

of hypocorticism was observed in 5 (15%), 3 (21%), and 2 (18%) patients, respectively. The risk of developing hypopituitarism symptoms in patients who previously had no such symptoms was low: hypogonadism developed in 1 (12.5%) patient; hypocorticism, in 1 (3%) patient; and hypothyroidism, in 1 (4%) patient. No cases of developing permanent diabetes insipidus were revealed. Moderate hyperprolactinemia was preoperatively observed in 16 (39%) patients; the blood PRL level decreased after the surgery in most patients and remained elevated in only one woman.

In patients with suprasellar meningiomas (group IV), hyperprolactinemia was observed preoperatively in 13 (31.7%) cases; the maximum PRL level was 4050 mU/l. After the surgery, moderate hyperprolactinemia persisted in only 2 (15%) out of 13 patients who had it preoperatively. Resection of suprasellar meningiomas not involving pituitary stalk transection was not accompanied by aggravation of hypopituitarism symptoms; diabetes insipidus persisted in one (2.4%) patient; no new cases of diabetes insipidus were reported.

In groups I and II of patients who had undergone pituitary stalk transection, hyperprolactinemia ( $p < 0.05$ ), hypocorticism ( $p < 0.05$ ), hypothyroidism ( $p < 0.05$ ), and hypogonadism ( $p < 0.05$ ) were observed significantly more frequently as compared to patients in groups III and IV who had undergone tumor resection without pituitary stalk transection.

Eight women of reproductive age with hyperprolactinemia and amenorrhea (2 women having craniopharyngiomas; 4 women having HFPA; and 2 women having meningioma) were preoperatively treated with cabergoline at a dose of 0.25 mg per week. In all of them, the PRL level (3 cases) or hypoprolactinemia (5 cases) was normalized before the surgery; recovery of menstrual cycle was observed in four patients (2 women having pituitary adenoma and 2 women having meningioma).

## DISCUSSION

The pituitary stalk is an anatomical structure consisting of the portal vessel system and axons of the hypothalamic nuclei terminating in the posterior pituitary lobe (Fig. 2).

Pathophysiology of the hypothalamo-hypophyseal system was thoroughly described in studies by I.I. Dedov, I.G. Akmaev, A.A. Voitkevich, V.N. Babichev [1–4], and other Russian and foreign authors.

Blood is supplied to the pituitary gland through branches of the internal carotid artery: the superior and inferior hypophyseal arteries [5]. The superior hypophyseal arteries enter the median eminence to form a capillary network and supply the hypothalamus (Figs. 2 and 3). These capillaries, which contact with axon terminals in small neurosecretory cells of the mediobasal hypothalamus, merge into the portal veins descending along the pituitary stalk into the adeno-hypophyseal pa-

renchyma and divide again into a network of sinusoid capillaries. Having passed through the median eminence, blood is enriched in hypothalamic releasing hormones and is eventually supplied to the anterior pituitary. Blood rich in adeno-hypophyseal hormones drains via a system of veins running into venous sinuses of the dura mater and further into the general circulation. Hence, the hypophyseal portal system with blood flowing down from the hypothalamus is a morphofunctional component of the complex mechanism for ensuring neurohumoral control of hypophysiotropic function. Secretion of pituitary hormones depends on the interplay between the hypothalamus, the portal veins, and hormone-secreting anterior pituitary cells.

Blood is also supplied to the anterior pituitary through the portal veins. The inferior hypophyseal arteries are involved in blood supply to the posterior pituitary; they contact with the neurosecretory axon terminals in large-cell hypothalamic nuclei and are located below the sellar diaphragm (Fig. 3).

Unlike secretion of other pituitary hormones that is mainly stimulated by hypothalamus, secretion of PRL is controlled by tonic inhibiting effect of dopamine that is produced by hypothalamus. It is believed that pituitary stalk rupture or mechanical compression of the portal vessels disrupts the transport of dopamine and releasing hormones and cause hyperprolactinemia and deficiency of other pituitary hormones.

Axons of the nuclei of supraoptic and paraventricular neurons of the hypothalamus secreting antidiuretic hormone (ADH) also pass along the pituitary stalk along with portal vessels. In the form of granules bound to neurophysin protein into a complex, ADH is transported via axons of the neurons terminating in the posterior pituitary, which acts as a reservoir of ADH. From this reservoir, the hormone is released into the systemic circulation (Fig. 2). Damage done to axons of the pituitary stalk as a result of neurotrauma, surgical transection, or pituitary stalk destruction by a tumor causes manifestation of diabetes insipidus [6].

Cases of congenital pituitary stalk interruption syndrome (PSIS) have been reported in literature. In patients with this syndrome, the pituitary stalk is not seen in the MR image; there is no signal from the posterior pituitary and is a hyperintense signal in the area of infundibular processes of the third ventricle [7]. Different authors interpreted this condition as ectopic posterior pituitary and pituitary stalk agenesis or as traumatic pituitary stalk rupture as a result of birth injury. Rare mutations in the *HESX1*, *LH4*, *OTX3*, and *SOX3* genes can be a reason for PSIS [8, 9]. Clinical presentation involves pituitary dwarfism as a result of growth hormone deficiency, either isolated or caused by other manifestations of hypopituitarism. In a larger-scale study involving 55 children with PSIS conducted in China, growth hormone deficiency was revealed in all patients; hypogonadotropic hypogonadism, in 95.8%; ACTH deficiency, in 81.8%; and sec-

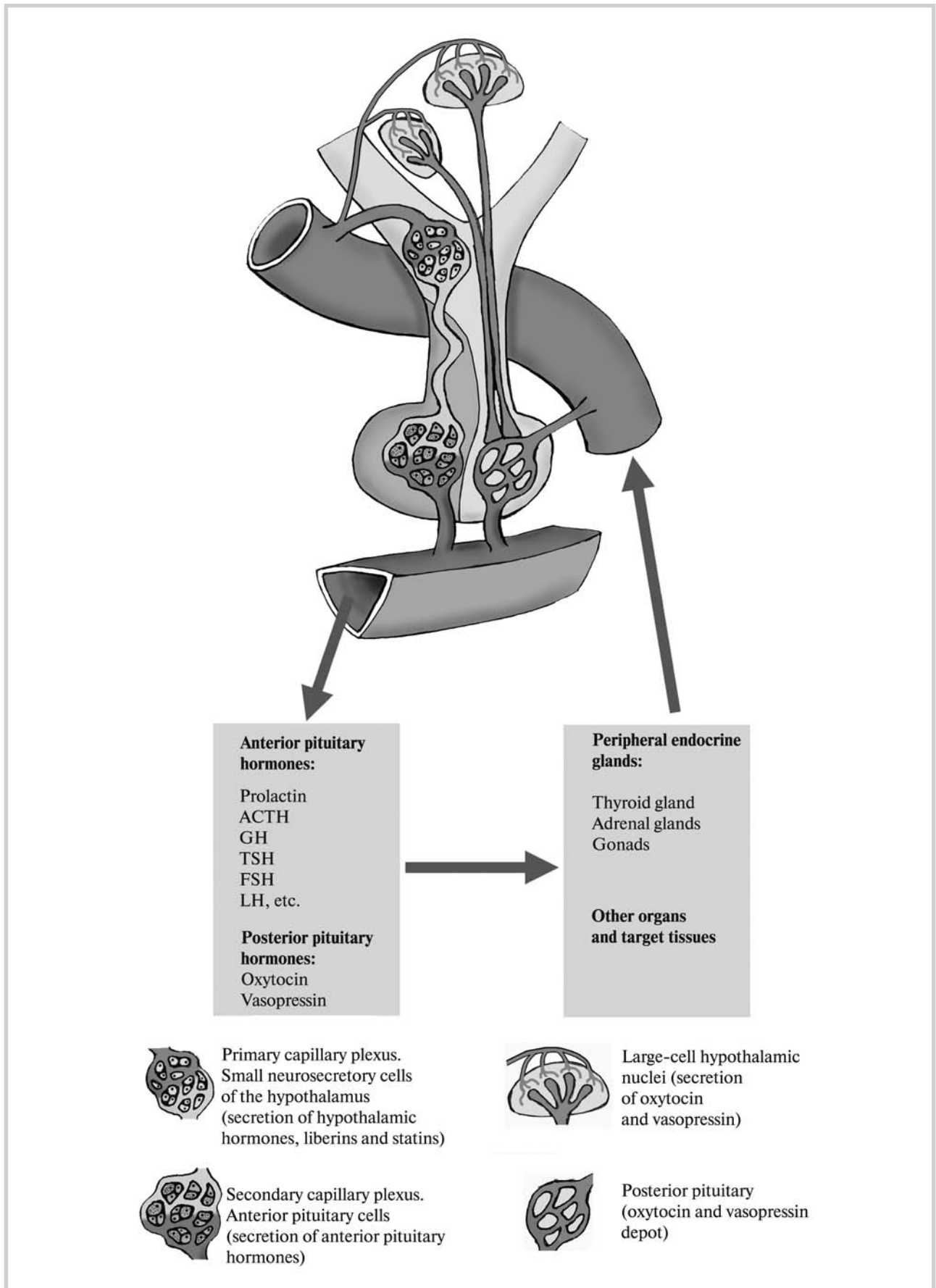


Fig. 2. Structure and function of the hypothalamus–pituitary gland–peripheral endocrine glands system (scheme).

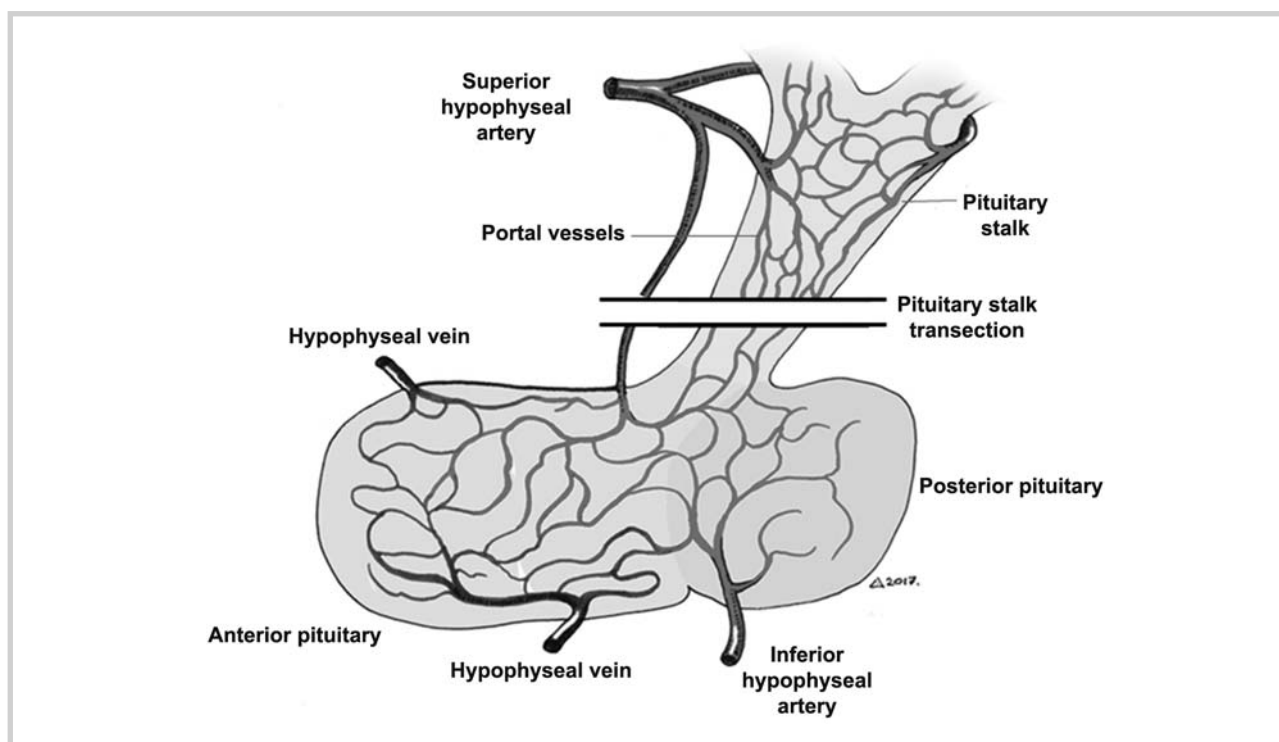


Fig. 3. The scheme of blood supply to the pituitary gland and blood vessel damage upon pituitary stalk transection.

ondary hypothyroidism, in 76.3% of patients. Hyperprolactinemia was observed in only 36.4% of cases [10].

The studies demonstrate that space-occupying processes in the chiasm-sellar region, such as pituitary macroadenomas [11], meningiomas [12], craniopharyngiomas [13], germinomas [14], gliomas, inflammatory processes (tuberculosis, sarcoidosis), metastases, and carotid artery aneurysms disturb secretion of pituitary hormones. Patients with portal vessel compression have moderate hyperprolactinemia and reduced secretion of pituitary hormones [11–15]. The PRL level in these cases is usually not higher than 2000 mU/l [16–18].

B.M. Arafah et al. showed that increased intrasellar pressure disturbing circulation of blood through the portal vessels is a significant mechanism in the pathogenesis of hyperprolactinemia and hypopituitarism upon space-occupying processes in the chiasm-sellar region. In patients with pituitary macroadenomas, intrasellar pressure can be as high as  $28.8 \pm 13.5$  mmHg (the normal intracranial pressure is less than 10–15 mmHg). In patients with hypopituitarism, intrasellar pressure is higher than in individuals with normal pituitary function. The PRL level was positively correlated with intrasellar pressure but not with tumor size. Recovery of pituitary function after adenectomy is possibly related to normalization of intrasellar pressure and recovery of circulation via the portal system. However, pituitary function is not recovered in some patients. Increased intrasellar pressure probably causes ischemic necrosis of the pituitary gland in this group of patients [19, 20].

In our study, preoperative hyperprolactinemia was revealed in 52 (37.4%) out of 139 patients with tumors in the chiasm-sellar region. In most cases, the PRL level was not higher than 2000 mU/l; only in two patients (with craniopharyngioma and meningioma) it was 3000 and 4050 mU/l, respectively.

Pituitary stalk compression in patients with pituitary adenomas and suprasellar meningiomas (groups II, III, and IV) did not lead to DI, while craniopharyngiomas originating from the pituitary stalk and destroying it (group I) were accompanied by DI in 23.9% of cases, possibly due to complete blockade of ADH transport or retrograde death of ADH-secreting hypothalamic cells.

Surgical tumor resection without pituitary stalk transection (groups III and IV) eliminated pituitary stalk compression and probably recovered transport of dopamine and releasing hormones of hypothalamus as evidenced by normalization of PRL levels in most patients and hypopituitarism regression in some patients. Similar results were obtained by H.A. Zaidi et al. who studied the pituitary function in 276 patients operated on through the transsphenoidal approach. The PRL level was normalized in 77.8% out of 72 patients preoperatively having hyperprolactinemia [21]. P. Nomikos et al. reported that the pituitary function recovered or was improved in 49.7% patients who had hypopituitarism before NFPA was resected through the transsphenoidal approach [22].

The literature lacks studies focusing on the transected pituitary stalk syndrome in humans. It has been demonstrated that pituitary stalk transection in animals re-

sults in profound atrophy of adrenal glands and gonads, less profound atrophy of the thyroid gland, and diabetes insipidus. Pituitary stalk transection noticeably slows down growth of young animals [23]. L. Vaughan et al. transected the pituitary stalk in 20 monkeys. LH was the first pituitary hormone to disappear from blood. The GH and cortisol levels significantly declined and were not increased after insulin injection. The PRL level increased and remained significantly elevated during the entire follow-up period (3 years), but some animals exhibited only moderate or transient hyperprolactinemia that was presumably related to revascularization of the anterior pituitary gland [24]. L.L. Anderson et al. evaluated the growth dynamics of calves with transected pituitary stalk. Neither pulsatile or reduced basal secretion of growth hormone was observed; blood levels of TSH and thyroid hormones were significantly reduced. Nevertheless, animals continued to grow, although at a very slow rate. Histological evaluation of the pituitary gland of the tested calves showed that it was significantly smaller than that in healthy animals. However, GH- and TSH-secreting cells remained in the pituitary tissue [25].

J.H. Adams showed in his review that pituitary stalk transection in animals (rats, sheep, and monkeys) causes extensive necrosis of the anterior lobe of the pituitary gland because of damage to the portal veins. However, a small portion of the pituitary gland tissue supplied with blood via the inferior hypophyseal arteries remains preserved. The absence of a barrier between the transected regions of the pituitary stalk could have caused revascularization and recovery of function of the anterior lobe of the pituitary gland [23].

In the 1950–1960s, hypophysectomy or pituitary stalk transection was performed at late stages of breast or prostate cancer, as well as in patients with progressive diabetic retinopathy. This surgery was believed to eliminate pain and to slow down progression of these diseases. J.H. Adams et al. described the anatomical changes in the pituitary gland in 21 patients (20 patients having breast or prostate cancer and one patient having diabetic retinopathy) after transcranial pituitary stalk transection. Tantalum or another inert material was placed between the transected ends of the pituitary stalk to prevent their union. All patients died postoperatively, within the period ranging between 30 hours and 11 months. Either infarctions or cicatrices in the anterior pituitary were detected in all these patients, but complete necrosis of this organ was never observed; a portion of the anterior pituitary parenchyma remained intact (to a different extent in different patients). The hormone-secreting cells in the intact area of the anterior pituitary were smaller than in the normal pituitary glands. The posterior lobe of the pituitary gland remained preserved but became smaller [26]. Unfortunately, the endocrine aspects were not discussed in this study.

Today, the effect of pituitary gland transection in patients with craniopharyngiomas can be evaluated indi-

rectly. Craniopharyngiomas are often preoperatively accompanied by endocrine disorders, which are aggravated after tumor resection regardless of tumor location and the surgical approach used. J.Honegger et al. [27] analyzed the endocrine disorders after resection of craniopharyngiomas. All patients developed panhypopituitarism and diabetes insipidus after pituitary stalk transection, while the risk of developing these disorders was lower when the pituitary gland was preserved, either completely or partially. However, the dynamics of the PRL level in patients who had undergone pituitary stalk transection was not described in this publication [27].

In our study, intraoperative pituitary stalk transection in patients with either preserved or compressed pituitary gland (groups I and II) led to development of panhypopituitarism in all patients and DI in most of them. Four (7%) of these patients did not have diabetes insipidus. The possible reason for this is that ADH was directly entering the systemic circulation without entering the posterior pituitary. The so-called ectopic posterior pituitary could have also been formed as a result of enlargement of the proximal end of the pituitary stalk. This phenomenon has been reported in studies involving patients who had undergone pituitary stalk transection near the pituitary diaphragm; if the pituitary stalk was transected near the hypothalamus, regression of DI is unlikely [28, 29].

In our study, pituitary stalk transection did not cause the anticipated aggravation of hyperprolactinemia. This condition was observed only in 21 (36.8%) out of 57 patients. In case of adenomas, this could be attributed to the intraoperative damage done to the residual posterior pituitary tissue but this situation also took place for patients with craniopharyngiomas, where the pituitary gland had been preserved.

Development of ischemia and necrosis of the pituitary gland are also possible. However, development of hypoprolactinemia will be expected in this case, but hypoprolactinemia was observed in our study only in 2 cases after resection of craniopharyngiomas and in one case after resection of NFPA. Therefore, it is also possible that either dopamine is transported to the posterior gland not only through the pituitary stalk or the integrity of portal vessels is partially restored.

Taking into account the differences in symptoms, two individual conditions (the pituitary stalk compression syndrome and the pituitary stalk transection syndrome) should be differentiated.

The pituitary stalk compression syndrome predominantly manifests itself as hyperprolactinemia (37.4% of cases); the frequency of hypopituitarism and diabetes insipidus in patients with preserved pituitary gland is low. In most cases, hyperprolactinemia is asymptomatic but can be accompanied by hypogonadism. Cabergoline therapy in these patients, even at minimum doses, rapidly leads to normoprolactinemia or hypoprolactinemia and recovery of sexual function. After the pituitary stalk



compression was eliminated, the PRL level is normalized due to recovery of dopamine transport. In patients with compression of both the pituitary stalk and the pituitary gland caused by suprasellarly growing adenomas, hypopituitarism symptoms are observed along with hyperprolactinemia symptoms. Elimination of compression of the pituitary gland and its stalk during adenoma resection recovers the pituitary function in 15–21% of cases; the remaining patients still have either partial or total hypopituitarism probably due to atrophy of hormone-secreting cells of the pituitary gland. A number of authors demonstrated that elevated preoperative PRL level is a predictor of recovery of pituitary function [22, 30]. Hence, P. Nomikos et al. analyzed the outcomes of surgical treatment of 621 patients with NFPA and observed either partial or complete regression of hypopituitarism symptoms in 80% of patients with the PRL level > 500 mU/l; in 52.3% of patients with the PRL level ranging from 100 to 500 mU/l; and in only 30% of patients with the PRL level < 100 mU/l [22].

The syndrome of neurosurgical pituitary stalk transection manifests itself as panhypopituitarism, DI, or hyperprolactinemia in 100, 93.0, and 36.8% of patients, respectively.

## CONCLUSIONS

This study has confirmed the role played by the pituitary stalk in transport of hypothalamic hormones via blood vessels and axons to the pituitary gland. We did not observe the anticipated elevation of PRL level after surgical transection of the pituitary stalk. Contrariwise, the frequency of development of hyperprolactinemia decreased in patients with NFPA and remained unchanged in patients with craniopharyngiomas. This suggests that a more detailed research into the reasons for elevation of PRL levels in patients with tumors in the chiasm-sellar region is needed. The findings that pituitary stalk transection leads to development or aggravation of panhypopituitarism symptoms in all patients and development of DI in most patients are relevant for neurosurgeons. Therefore, one should adhere to the tactics of preserving the pituitary stalk during neurosurgeries.

### SUPPLEMENTARY INFORMATION.

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#### ИНФОРМАЦИЯ ОБ АВТОРАХ

\*Астафьева Людмила Игоревна — д.м.н. [Ludmila I. Astafyeva, MD, PhD]; адрес: Россия, 125047, Москва, ул. 4-я Тверская-Ямская, 16 [address: 16, 4th Tverskaya-Yamskaya street, Moscow, 125047, Russia]; ORCID: <http://orcid.org/0000-0003-4480-1902>; eLibrary SPIN: 4209-4723; e-mail: Last@nsi.ru

Кадашев Борис Александрович — д.м.н., проф. [Boris A. Kadashev, MD, PhD, Professor]; ORCID: <http://orcid.org/0000-0001-8344-3381>; eLibrary SPIN: 4157-6654; e-mail: kadashev@nsi.ru

Калинин Павел Львович — д.м.н. [Pavel L. Kalinin, MD, PhD]; ORCID: <http://orcid.org/0000-0001-9333-9473>; eLibrary SPIN: 1775-7421; e-mail: PKalinin@nsi.ru

Кутин Максим Александрович — к.м.н. [Maxim A. Kutin, MD, PhD]; ORCID: <http://orcid.org/0000-0002-6520-4296>; eLibrary SPIN: 2336-5946; e-mail: kutin@nsi.ru

Клочкова Ирина Сергеевна [Irina S. Klochkova, MD]; ORCID: <http://orcid.org/0000-0002-7440-4687>; eLibrary SPIN: 8313-0190; e-mail: IKlochkova@nsi.ru

Фомичев Дмитрий Владиславович — к.м.н. [Dmitry V. Fomichev, MD, Ph.D]; ORCID: <http://orcid.org/0000-0002-5323-1000>; eLibrary SPIN: 3516-3513; e-mail: dfomichev@nsi.ru

Шарипов Олег Ильдарович — к.м.н. [Oleg I. Sharipov, MD, PhD]; ORCID: <http://orcid.org/0000-0003-3777-5662>; eLibrary SPIN: 3279-0844; e-mail: osharipov@nsi.ru

Андреев Дмитрий Николаевич — к.м.н. [Dmitry N. Andreev, MD]; ORCID: <http://orcid.org/0000-0001-5473-4905>; eLibrary SPIN: 8516-7994; e-mail: dandreev@nsi.ru

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