

УДК 616.216.3-002.3

DOI: 10.35693/2500-1388-2020-5-1-17-22

## Isolated lesions of the sphenoid sinus: features of diagnosis and treatment

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### Abstract

**Aim** – to analyze the cases of isolated lesions of the sphenoid sinuses and to identify the main errors in the differential diagnosis in the prehospital and treatment periods.

**Material and methods.** The study includes the data on the treatment of 58 patients with an isolated lesion of the sphenoid sinus in the period 2015–2018. The patients' age varied from 18 to 68 years. Gender distribution: men – 21 (30.7%), women – 37 (69.3%).

**Results.** The following surgical approaches were used: transnasal access, extended transnasal access, transtymoid access, access according to the Bolger Box technique. In one case, the transpterygoid approach was used. When performing extended access, it was possible to achieve the formation of persistent, epithelized anastomosis in all the cases. In polypous-purulent forms of sphenoiditis, the relapses of the disease were most often observed, however, only anti-inflammatory therapy was required, including a sinus irrigation through the formed anastomosis.

**Conclusion.** Further studies are required, to examine the features/safety and clinical efficacy of the various endosurgical approaches.

**Keywords:** sphenoid sinus, symptom complex, latent sphenoiditis, X-ray examination, endorhinotomy, endosurgical treatment methods.

**Conflict of interest:** nothing to disclose.

### Citation

Larin RA, Shakhov AV, Krasilnikova SV, Suzaeva PV, Pisarev EN. **Isolated lesions of the sphenoid sinus: features of diagnosis and treatment.** *Science & Innovations in Medicine.* 2020;5(1):17-22. doi: 10.35693/2500-1388-2020-5-1-17-22

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Received: 14.01.2020

Revision Received: 10.02.2020

Accepted: 11.02.2020

## Изолированные поражения клиновидной пазухи: особенности диагностики и лечения

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### Аннотация

**Цель** – анализ случаев изолированного поражения клиновидной пазухи, выявление основных ошибок при дифференциальной диагностике на догоспитальном этапе и на этапах лечения.

**Материал и методы.** В работе приведены данные о лечении 58 пациентов с изолированным поражением клиновидной пазухи в период 2015–2018 гг. Возраст пациентов от 18 до 68 лет. Среди них было 37 (69,3%) женщин и 21 (30,7 %) мужчина.

**Обсуждение и результаты.** Применялись следующие хирургические доступы: трансназальный, расширенный трансназальный, трансмаксиллярный, доступ по методике Bolger Box, транскрило-видный (в одном случае). При выполнении расширенного доступа удалось добиться формирования стойкого, эпителизированного соустья во всех случаях. При полипозно-гнойных формах сфеноидита наиболее часто наблюдались рецидивы заболевания, однако здесь требовалась только противовоспалительная терапия, в т.ч. орошение пазухи через сформированное соустье.

**Выводы.** Необходимы дальнейшие исследования с целью изучения особенностей/безопасности и клинической эффективности различных эндохирургических доступов.

**Ключевые слова:** клиновидная пазуха, симптомокомплекс, латентный сфеноидит, лучевое исследование, эндоринотомия, методы эндохирургического лечения.

**Конфликт интересов:** не заявлен.

### Для цитирования:

Ларин Р.А., Красильникова С.В., Шахов А.В., Сузаева П.В., Писарев Е.Н. **Изолированные поражения клиновидной пазухи: особенности диагностики и лечения.** *Наука и инновации в медицине.* 2020;5(1):17-22. doi: 10.35693/2500-1388-2020-5-1-17-22

КТ – компьютерная томография; МРТ – магнитно-резонансная томография; КП – клиновидная пазуха; ОНП – оболочка носовых пазух.

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Рукопись получена: 14.01.2020

Рецензия получена: 10.02.2020

Решение о публикации принято: 11.02.2020

## ■ INTRODUCTION

The spread of radiation (magnetic resonance imaging (MRI), Computed tomography (CT)) and visual (endoscopy) diagnostic methods observed today is responsible for an increase in the number of cases of isolated sphenoiditis [1, 2, 3]. According to the literature, the proportion of isolated sphenoiditis in the general structure of diseases of the paranasal sinuses (PNS) is no more than 5% [4, 5, 6]. However, taking into account the huge number of cases of PNS inflammatory pathology, the absolute figures can be very significant. In the structure of sinusitis, there are increasingly resistant (resistant to treatment) forms, including those of fungal origin [7]. Data on the prevalence of the pathology are very scarce, as sphenoiditis is rarely presented as an independent nosological entity when performing a statistical report in hospitals and clinics. The relatively low prevalence often determines the passive position of specialists in the differential diagnosis of sphenoid sinus (SS) lesions. CT and MRI are the main methods used for the differential diagnosis in this group of patients. The interpretation of the research results is however not always unambiguous and can lead to both the overdiagnosing and, conversely, to the underdiagnosing of sphenoiditis, expressed as an underestimation of the radiation diagnosis data and as an objective presentation, often leading to the development of chronic and complicated forms.

Patients are referred to an ENT doctor only after a long, unsuccessful treatment with specialists of related specialties, and this explains the frequent underdiagnosis of sphenoiditis, and the occurrence of complicated forms [8]. Differential diagnosis of the pathological process in the sinus at the preoperative stage is extremely important, as ill-considered intervention can cause severe and even fatal complications [9, 10].

Approximately, 5%–30% of all isolated lesions of the sphenoid sinus are seen in patients with the non-invasive fungal form [11, 12]. Chronic sphenoiditis is characterized by a latent course, not always diagnosed in the early stages [13, 14]. According to a number of researchers, the frequency of pathological findings in the sphenoid sinus during autopsy of persons, whose lifetime diagnosis of sphenoiditis has not been established, ranges from 10% to 68% [15, 16]. It is very important to study the issues of remodeling in the sphenoid sinus, including the phenomena of osteitis in the fungal forms [17].

Complicated course of isolated sphenoiditis is not uncommon, and the main factor in the development of complications is a delayed diagnosis. However, complications associated with the involvement of the oculomotor nerves in the pathological process, especially pair VI (*n. abducens*), are the most common [4, 9, 16]. Literature provides cases of invasive, generalized forms of fungal sphenoiditis with the rapid development of ophthalmic, intracranial, and systemic (septic) complications [7, 12, 14].

According to the literature, treatment approaches for isolated lesions of the sphenoid sinus are different. Some authors consider the presence of isolated sphenoiditis, especially fungal forms like mucocoele, an absolute indication for surgery, while others start with a conservative therapy in the absence of complications [1, 3, 11, 12]. The surgical treatment in such patients is not only aimed at stopping the inflammatory process, but also at creating the conditions for adequate ventilation of the sinuses, thereby preventing possible relapse. Issues of the differentiated approach to the surgical treatment are insufficiently covered in the scientific literature and are predominantly descriptive.

## ■ AIM

The study aimed to analyze cases of isolated lesions of the sphenoid sinuses and to identify the main aspects and errors in the differential diagnosis at the prehospital stage.

## ■ MATERIAL AND METHODS

The paper provides data on the treatment of 58 patients with isolated lesions of the sphenoid sinus, who were hospitalized at the N.A. Semashko Nizhny Novgorod Regional Clinical Hospital (Department of Ear, Throat and Nose Diseases of the Privolzhsky Research Medical University of the Ministry of Health of the Russian Federation) during a four years period, from 2015–2018. Their ages ranged between 18 and 68 years. The average age of patients with isolated sphenoiditis was 43 years old; women under 35 were the most concerned. Sex distribution showed 21 (30.7%) men and 37 (69.3%) women. The disease duration was  $26 \pm 19$  days. A total of 118 patients with various forms of damage to the sphenoid sinus were monitored in the clinic during this period with an SS lesion registered as a manifestation of chronic rhinosinusitis (with and without polyps) in 60 patients, meaning there was a combined lesion of several or all of the PNS even though such cases were not included in the study.

*Inclusion criteria* were X-ray (CT, MRI) signs of a pathological process in the sphenoid sinus, specific and nonspecific symptoms, latent course of sphenoiditis, and absence of a pathological process in other PNS.

*Exclusion criteria* were combined lesion of other groups of PNS, and nosocomial sphenoiditis.

Conditions such as curvature of the nasal septum, vasomotor/allergic rhinitis, turbinate hypertrophy, *conchabullosa* of the middle turbinate were not exclusion criteria.

Patients with newly established diagnosis accounted for 85% of the total; recurrent forms of the disease were noted in 15% of cases, including 5 patients after previous surgery (**Table 1**).

Upon admission to the hospital, patient examination was performed, including clinical analyzes, consultations of related specialists, namely

Morphological form	Number of cases
Polypous process	15 (25.8%)
Cyst	18 (31%)
Mucocele	5 (8.6%)
Fungal sphenoiditis	12 (20.6%)
Invasive fungal sphenoiditis	2 (3.4%)
Meningocele	4 (6.8%)
Neoplasm	2 (3.4%)

**Таблица 1.** Распределение по виду патологического процесса  
**Table 1.** Distribution by the type of pathological process

a neurologist, a neurosurgeon, an ophthalmologist (depending on clinical manifestations). All patients underwent preoperative endoscopy. In preparation for surgical treatment, the presence of concomitant diseases in the patient was assessed through the manifestation of symptoms in PNS affecting significantly the course of the pathological process in the nasal cavity like bronchial asthma, aspirin triad, persistent or intermittent allergic rhinitis, as well as a combination of these diseases.

## DISCUSSION AND RESULTS

Cephalic syndrome in most cases was the main reason for seeking medical help. All patients with pain syndrome were initially examined by a neurologist or therapist; they underwent an MRI scan at the prehospital stage. In this group (n = 21, 36.2%), 9 patients were referred to an otorhinolaryngologist immediately after receiving MRI data. 12 patients either underwent further conservative treatment by a neurologist or did not receive any treatment, despite the obvious data of MRI studies. After the MRI study, a clarifying CT scan was prescribed for only 3 patients with the rest of patients being referred to the hospital with MRI results. We can therefore suggest within the framework of our study, the prevalence of MRI diagnostics in prehospital examination and the neglect of CT studies by specialists. The symptomatic presentation in the patients studied varied greatly

from latent asymptomatic forms to severe cephalic and ophthalmic manifestations. We noted a certain relationship between symptomatic manifestations and the morphological forms of the disease (**Table 2**).

Manifesting rhinological symptoms were generally noted in no more than one third of cases. In other situations, either nonspecific symptoms (cephalgic and/or ophthalmoplegic manifestations) or asymptomatic courses were registered. Latent forms of SS lesions detected accidentally during MRI/CT examination accounted for about 20% of all cases. These lesions were most often in the form of a cyst of the sphenoid sinus and mucocele (Figure 1) and were less often asymptomatic in the fungal form of the lesion and meningocele (**Figures 2, 3**).

**Surgery.** All patients underwent surgical treatment after a thorough analysis of CT scans conducted to clarify the variant of the sphenoid sinus structure and the presence of anatomical variants of the structure (Onodi cells, digiscence of the canal of the internal carotid artery, optic nerve, etc.) (**Figures 4a, 4b**).

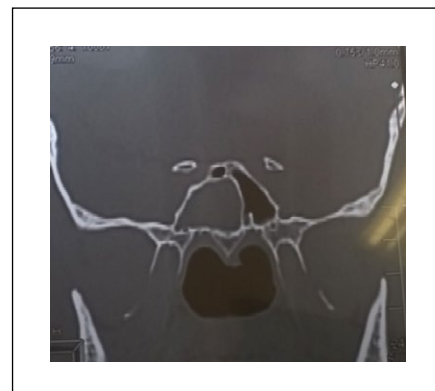
All surgical interventions were performed under general anesthesia. The transnasal, extended transnasal, transthemoid, Bolger Box approaches were the most frequently used although the transpterygoid approach was used in one case (**Table 3, Figure 5, 6**).

Expanded access (P.J. Wormald 2005, J.N. Palmer 2013), in contrast to the traditional one with mechanical expansion of the natural anastomosis, involves cutting out a short (5–10 mm) nasoseptal mucosal graft below and medially to the sinus anastomosis on a pedicle fed from the posterior septal branch of the pterygopalatine artery with a wide exposure and resection of the anterior wall of the sinus. We also expanded the anastomosis using a cutter. This method simplifies the process in case the natural anastomosis is not visualized or is not technically available and/or there is a need for a wide opening of the sinus. A pedicle graft is used to close a wide bone defect, which promotes its further epithelialization and minimizes the development of osteitis in the future. Studies by a number of authors indicate that transthemoidal and transnasal approaches can equally

Morphological form	Clinical symptoms				
	Headache	Postnasal drip	Dizziness	Nasal obstruction	Orbital symptoms
Polypous/polypous-purulent process	+	+++	-	++	-
Cyst	-	-	-	+	-
Mucocele	++	+	-	+	-
Fungal sphenoiditis	++	++	+	+	+
Invasive fungal sphenoiditis	+++	++	+	+	+++
Meningocele	+	+	+	-	-
Neoplasm	++	+	+	-	+++

«+» – severity of the symptom from + to +++. «-» – absence of symptom.

**Таблица 2.** Симптоматические проявления  
**Table 2.** The symptomatic manifestation



**Рисунок 1.** Мукоцеле клиновидной пазухи.

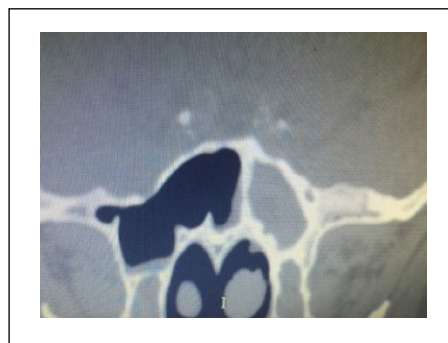
**Figure 1.** Mucocele of the sphenoid sinus.





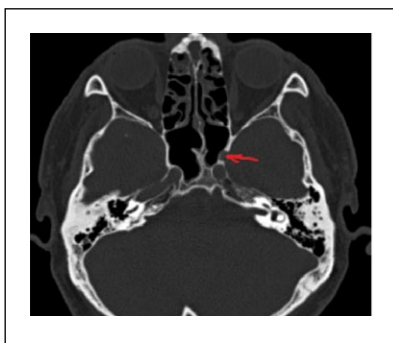
**Рисунок 2.** Грибковый сфеноидит. 2.1 КТ (аксиальный срез); 2.2 Соустье obturировано полипом. Трансназальный доступ; 2.3 – грибковые массы в пазухе.

**Figure 2.** Fungal sphenoiditis. 2.1 CT (axial cross-section); 2.2 Anastomosis is obturated by a polyp. Transnasal access; 2.3 – fungal masses in the sinus.



**Рисунок 3.** КТ (фронтальный срез). Остеит стенок клиновидной пазухи при грибковом синусите.

**Figure 3.** CT (front section). Osteitis of the walls of the sphenoid sinus in fungal sinusitis.



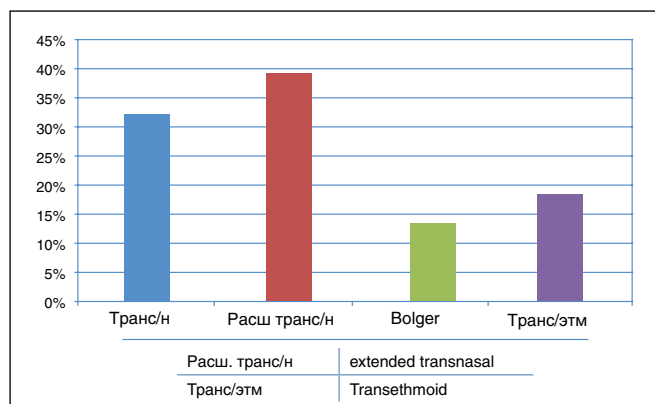
**Рисунок 4а.** Дигисценция канала внутренней сонной артерии. КТ-исследование.

**Figure 4a.** Dehiscence of the internal carotid artery channel. CT study



**Рисунок 4б.** Дигисценция канала внутренней сонной артерии. Эндоскопическая картина.

**Figure 4b.** Dehiscence of the internal carotid artery channel. Endoscopic image.



**Таблица 3.** Виды хирургических вмешательств  
**Table 3.** Types of surgical interventions

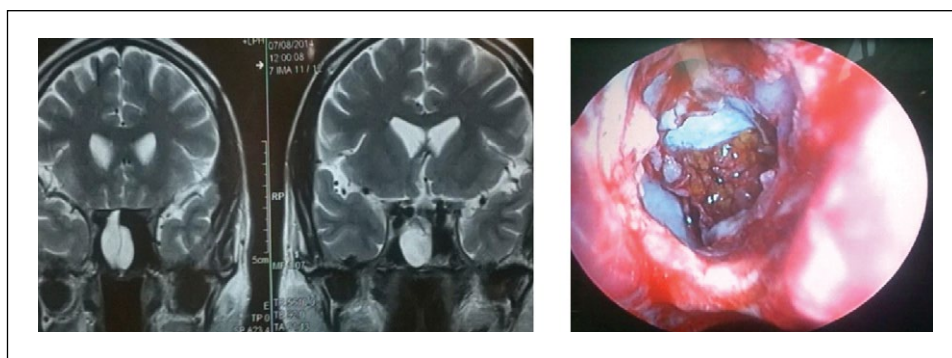
be used in isolated sinus lesions. The transnasal approach is safer than the transtethmoidal and is the method of choice for isolated sinus involvement, provided that the pathological process in the sinus does not require extensive revision and/or the creation of a sufficient volume of fenestration in situations of high risk of recurrence.

There were no complications in the postoperative period. On days 5–7, all patients underwent endorinoscopy. Control CT was performed in 11 patients within 2 to 3 months; the rest of the patients (from remote areas) however did not undergo the control examination. When performing an extended approach, the formation of a persistent, epithelized



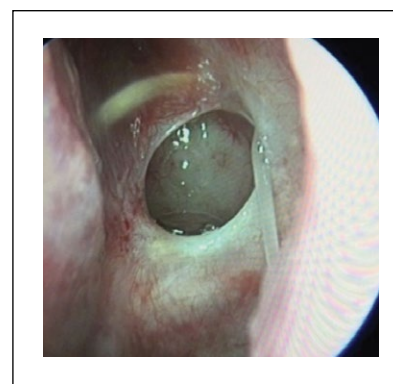
**Рисунок 5.** 5а – грибковое тело латерального кармана клиновидной пазухи (КТ, аксиальный срез); 5б – расширенный трансназальный доступ (70° эндоскоп); 5с – КТ через 6 мес. после операции.

**Figure 5.** 5a – fungal ball in the lateral "pocket" of the sphenoid sinus (CT, axial section); 5b – extended transnasal access (70° endoscope); 5c – CT in 6 months after operation.



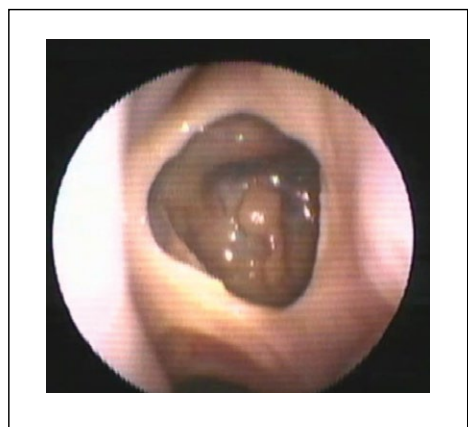
**Рисунок 6.** Менингоцеле клиновидной пазухи. 6a – МРТ (фронтальный срез); 6b – расширенный трансназальный доступ. Пластика ликворного дефекта после удаления менингоцеле (материал – жир).

**Figure 6.** Meningocele of the sphenoid sinus. 6a – MRI (frontal section); 6b – extended transnasal access. Plasty of the liquor defect after the meningocele removal (the material – fat).



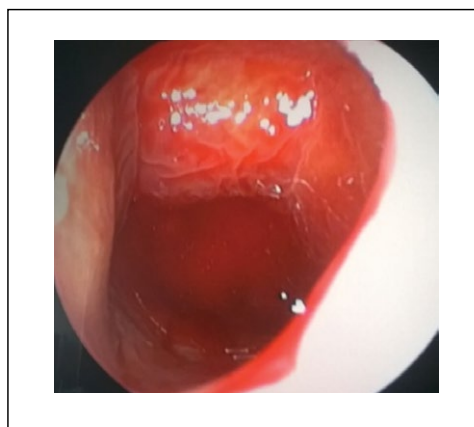
**Рисунок 7.** Соустье через 1 год после расширенного доступа.

**Figure 7.** Anastomosis 1 year after expanded access.



**Рисунок 8.** Соустье через 3 года после расширенного трансназального доступа.

**Figure 8.** Anastomosis 3 years after expanded access.



**Рисунок 9.** Рецидив полипозно-гнойного сфеноидита через 6 месяцев после операции.

**Figure 9.** Recurrence of polypous-purulent sphenoiditis in 6 months after surgery.

## CONCLUSIONS

Isolated sphenoiditis amounted to 3% in the structure of patients who underwent endosurgical treatment for PNS pathology (approximately 30% of the total number of sphenoiditis). In the hospital, patients with a diagnosis of isolated sphenoiditis established precisely at the prehospital stage accounted for no more than 12% of the total, and this may either be due to underdiagnosis, a passive position in relation to the

anastomosis was possible to achieve in all cases (**Figures 7, 8**). With polypous-purulent forms of sphenoiditis, relapses of the disease were most often registered, requiring only anti-inflammatory therapy and irrigation of the sinus through the formed anastomosis (**Figure 9**).

The incidence of adhesive process after interventions was approximately 20%, while cicatricial adhesion caused by the recurrence of the pathological process and requiring revision intervention was seen in three cases only. In one of the cases, a patient with a history of sphenotomy for chronic sphenoiditis was identified to have the Onodi cell, in which the fungal inflammation was localized, not opened (recognized), and required repeated surgery.

pathology of the sphenoid sinus in outpatient doctors, or caused by approach errors. The predominance of MRI diagnosis in prehospital examination and the ignorance of CT studies by specialists were noted.

Surgery was the main method of treatment for isolated sphenoiditis, with the extended transnasal approach being the most commonly used. The combination with drug treatment in the postoperative period is however required.

Further studies are necessary to study the aspects, safety and clinical efficacy of various endosurgical approaches. ■

**Conflict of interest.** The authors declare no conflict of interest.

## ЛИТЕРАТУРА / REFERENCES

1. Karpischenko SA, Dolgov OI, Stancheva OA. Our experience of endoscopic surgical treatment of isolated sphenoiditis. *Russian rhinology*. 2014;2:16–17. (In Russ.). [Карпищенко С.А., Долгов О.И., Станчева О.А. Опыт эндоскопического хирургического лечения изолированных сфеноидитов. *Российская ринология*. 2014; 2:16–17].
2. Piskunov GZ. Clinical rhinology. M., 2006. (In Russ.). [Пискунов Г.З. Клиническая ринология. М., 2006].
3. Chung L. The possible failing reasons of balloon catheter dilation procedure in the management of chronic rhinosinusitis. *Laryngoscope*. 2018;32(5):336–341. doi: 10.13201/j.issn.1001-1781.2018.05.005

4. Karpischenko SA. Pain syndrome in patients with isolated sphenoiditis: our experience in diagnosis and treatment. *Folia Otorhinolaryngologia et Pathologiae Espiratoriae*. 2017;2:4–10. (In Russ.). [Карпищенко С.А. Болевой синдром при изолированном сфеноидите: наш опыт в диагностике и лечении. *Folia Otorhinolaryngologia et Pathologiae Espiratoriae*. 2017;2 :4–10].
5. Chen Y, Qiu L, Qiu J. Diagnosis and endoscopic treatment of isolated sphenoid sinus disease. *Lin Chung*. 2014;28 :760–763. PMID: 25219196
6. Fokkens J, Lund V. European Position Paper on Rhinosinusitis and Nasal Polyps. *Rhinology*. 2012;23:329. PMID: 22764607
7. Bhandary S, Bhat V. A case of sphenoid sinus mucocoele following endoscopic sinus surgery for fungal sinusitis. *NUJHS*. 2013;3:117–119.
8. Moss WJ, et al. Isolated sphenoid sinus opacifications: a systematic review and meta-analysis. *Int Forum Allergy Rhinol*. 2017;7(12):1201–1206. doi: 10.1002/alr.22023
9. Fawaz SA, Ezzat WF, Salman MI. Sensitivity and specificity of computed tomography and magnetic resonance imaging in the diagnosis of isolated sphenoid sinus diseases. *Laryngoscope*. 2011;121(7):1584–9. doi: 10.1002/lary.21828
10. Kapitanov DN, Lopatin AS. The use of the navigation system in endoscopic surgery of the paranasal sinuses and the base of the skull. *Vestnik otorhinolaryngologii*. 2005;2:12–17. (In Russ.). [Капитанов Д.Н., Лопатин А.С. Применение навигационной системы в эндоскопической хирургии околоносовых пазух и основания черепа. *Вестник оториноларингологии*. 2005;2:12–17].
11. Polev GA. The giant fungal body of the sphenoid sinus with the destruction of the base of the skull. *Vestnik otorhinolaryngologii*. 2012;3:96–98. (In Russ.). [Полев Г.А. Гигантское грибковое тело клиновидной пазухи с деструкцией основания черепа. *Вестник оториноларингологии*. 2012;3:96–98].
12. Karpischenko SA. Complications of endoscopic sphenotomy. *Materials congress of rhinologists*. Suzdal, 2016:29. (In Russ.). [Карпищенко С.А. Осложнения эндоскопической сфенотомии. *Материалы конгресса ринологов*. Суздаль, 2016:29].
13. Mareev GO, Geyvondyan ME. Anatomical structure of sinus sphenoidalis in skull system. *Bulletin of Medical Internet Conferences*. 2014;5:669–676. (In Russ.). [Мареев Г.Н., Гейвондян М.Э. Клиновидная пазуха в системе черепа и ее анатомические особенности. *Бюллетень медицинских интернет-конференций*. 2014;5:669–676].
14. Gayvoronskiy AI, Gayvoronskiy IV, Yakovleva A.A. Characteristics of the structure and relief of the sphenoidal sinus walls (endovideoscopy data). Study notes. First Pavlov State Medical University of St. Petersburg. 2011;XVIII:46–49. (In Russ.). [Гайворонский А.И., Гайворонский И.В., Яковлева А.А. Особенности строения и рельефа стенок клиновидной пазухи по данным эндовидеоскопии. Учебные записки СПбГМУ им. акад. И.П. Павлова. 2011;XVIII:46–49].
15. Nishanth S, Nandeesh B. Isolated sphenoid Sinus Lesions: Experience with a few rare pathologies. *J Neurosci Rural Pract*. 2017;8(1):107–113. doi: 10.4103/0976-3147.193540
16. Vereschagina OE, Dolgov OI, Stancheva OA. Transnasal endoscopic approach in treatment of isolated sphenoiditis. *Russian otorhinolaryngology*. 2015;1:26–29. (In Russ.). [Верещагина О.Е., Долгов О.И., Станчева О.А. Трансназальный эндоскопический подход в лечении изолированных сфеноидитов. *Российская оториноларингология*. 2015;1:26–29].
17. Tush EV, Eliseeva TI, Khaletskaya OV, et al. Extracellular Matrix Markers and Methods for Their Study (Review). *Sovremennye tehnologii v medicine*. 2019;11(2):133–149. (In Russ.). [Туш Е.В., Елисеева Т.И., Халецкая О.В. и др. Маркеры состояния экстрацеллюлярного матрикса и методы их исследования (обзор). *Современные технологии в медицине*. 2019;11(2):133–149]. doi.org/10.17691/stm2019.11.2.20