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ДИФФЕРЕНЦИАЛЬНЫЙ ДИАГНОЗ ПНЕВМОНИИ ПРИ НАЗАЛЬНОЙ ЛИКВОРЕЕ В УСЛОВИЯХ ПАНДЕМИИ COVID-19

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Differential Diagnosis of Pneumonia as a Complication of Nasal Liquorrhea in the Context of the COVID-19 Pandemic

Резюме

Назальная ликворея — истечение цереброспинальной жидкости из ликворных пространств полости черепа в полость носа или околоносовые пазухи вследствие наличия врожденного или приобретенного дефекта костей основания черепа и мозговых оболочек различной этиологии. Назальная ликворея приводит к потенциально смертельным осложнениям: менингит, менингоэнцефалит, пневмоцефалия, абсцесс мозга. Также при назальной ликвореи возможно возникновение менее опасных осложнений: аспирационного пневмонита и гастрита. В статье приводится случай аспирационного пневмонита у двух пациентов с назальной ликвореей, проходившими лечение в НМИЦН им. Н.Н. Бурденко во время пандемии COVID-19. Оба пациента отмечали профузный характер назальной ликвореи, жаловались на кашель в горизонтальном положении. В обоих случаях в ходе выполнения полимеразной цепной реакции РНК вируса (SARS-CoV-2) не обнаружена. Антитела (IgG, IgM) к коронавирусу не выявлены. На компьютерной томографии органов грудной клетки в обоих случаях выявлены участки затемнения по типу «матовое стекло». Так как данных за коронавирусную инфекцию не получено (отрицательные тесты на коронавирус, отсутствие антител), изменения в легких были интерпретированы как следствие постоянной аспирации ликвора. Пациентов госпитализировали в отдельную палату. Обоим пациентам проведена эндоскопическая эндоназальная пластика дефекта основания черепа. Послеоперационный период в обоих случаях протекал без особенностей. В обоих случаях пациенты выполнили через месяц компьютерную томографию органов грудной клетки. На снимках признаки поражения легочной ткани полностью регрессировали.

Ключевые слова: *назальная ликворея, дефект основания черепа, аспирационный пневмонит, основание черепа*

Конфликт интересов

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Abstract

Nasal liquorrhea — the outflow of cerebrospinal fluid from the cerebrospinal fluid spaces of the cranial cavity into the nasal cavity or paranasal sinuses due to the presence of a congenital or acquired defect in the bones of the skull base and meninges of various etiologies. Nasal liquorrhea leads to potentially fatal complications: meningitis, meningoencephalitis, pneumocephalus, brain abscess. Also, with nasal liquorrhea, less dangerous complications may occur: aspiration bronchopneumonia and gastritis. The article presents a case of aspiration pneumonitis in two patients with nasal liquorrhea treated at the N.N. N.N. Burdenko during the COVID-19 pandemic. Both patients noted the profuse nature of the nasal liquorrhea, complained of coughing in a horizontal position. In both cases, no RNA virus (SARS-CoV-2) was detected during the polymerase chain reaction. Antibodies (IgG, IgM) to coronavirus were not detected. Computed tomography of the chest organs in both cases revealed areas of frosted glass darkening. Since no data was obtained for coronavirus infection (negative tests for coronavirus, lack of antibodies), changes in the lungs were interpreted as a consequence of constant aspiration of cerebrospinal fluid. The patients were admitted to a separate ward. Both patients underwent endoscopic endonasal plasty of the skull base defect. The postoperative period in both cases was uneventful. In both cases, the patients underwent computed tomography scan of the chest organs one month later. On the photographs, the signs of pneumontis completely regressed.

Key words: *nasal liquorrhea, skull base defect, aspiration pneumonitis, skull base*

Conflict of interests

The authors declare no conflict of interests

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CT — computed tomography, TBI — traumatic brain injury

Introduction

Cerebrospinal fluid (CSF) rhinorrhea is the outflow of cerebrospinal fluid from the cerebrospinal fluid spaces of the cranial cavity into the nasal cavity or paranasal sinuses due to a congenital or acquired defect in the bones of the skull base and meninges of various etiologies [1].

CSF rhinorrhea leads to potentially fatal complications: meningitis, meningoencephalitis, pneumocephalus, brain abscess. CSF rhinorrhea can also cause less dangerous complications: aspiration pneumonitis and gastritis [2, 3]. With a pronounced outflow of cerebrospinal fluid in patients in a supine position, the cerebrospinal fluid often enters the lower respiratory tract through the nasal cavity and nasopharynx. In this case, aspiration pneumonitis occurs. Patients complain of cough that occurs mainly in the supine position [4].

Pneumonitis is a disease characterized by damage to the tissues that support the intralobular gas exchange and form pulmonary key structures — the alveoli. According to ICD-10, there are several types of pneumonitis:

J.67 — J.67.9 Hypersensitivity pneumonitis due to organic dust.

J68.0 Respiratory conditions due to inhalation of chemicals, gases, fumes and vapors.

J69 Pneumonitis due to solids and liquids.

The fundamental difference between pneumonitis and pneumonia is associated with etiology. In pneumonia, inflammation is caused by infectious agents such as bacteria, viruses, or fungi. The onset of pneumonitis is not associated with the above-listed infections, and inflammation is immunologically mediated [5]. Aspiration pneumonitis, triggered by the ingress of stomach contents into the lower respiratory tract (Mendelson syndrome) and also occurring after intubation, stands out [6]. In CSF rhinorrhea, cerebrospinal fluid enters the lungs in the supine position, which also causes symptoms of pneumonitis.

Differential diagnosis of pneumonitis is carried out with viral pneumonias, which are seasonal and occur mainly in winter. In December 2019, an epidemic of novel coronavirus disease caused by SARS-CoV-2 broke out in Wuhan (China) and rapidly spread across the world [7]. In February 2020 (02/12/2020), WHO officially named the infectious disease COVID-19 (Coronavirus disease 2019). The International Committee on Taxonomy of Viruses officially named the causative agent of the disease SARS-CoV-2 [8]. The main manifestation of the disease is pneumonia. There is also an asymptomatic or mild course with the involvement of the upper respiratory tract, which resolves within a week after infection [9]. According to the Internet resource https://www.worldometers.info/coronavirus as of January 31, 2021, the number of infected people exceeded 103 million; the death rate was approximately 2.2 million. In Russia, 3,850,439 cases of COVID-19 had been recorded; the death rate was 73,182 people [10].

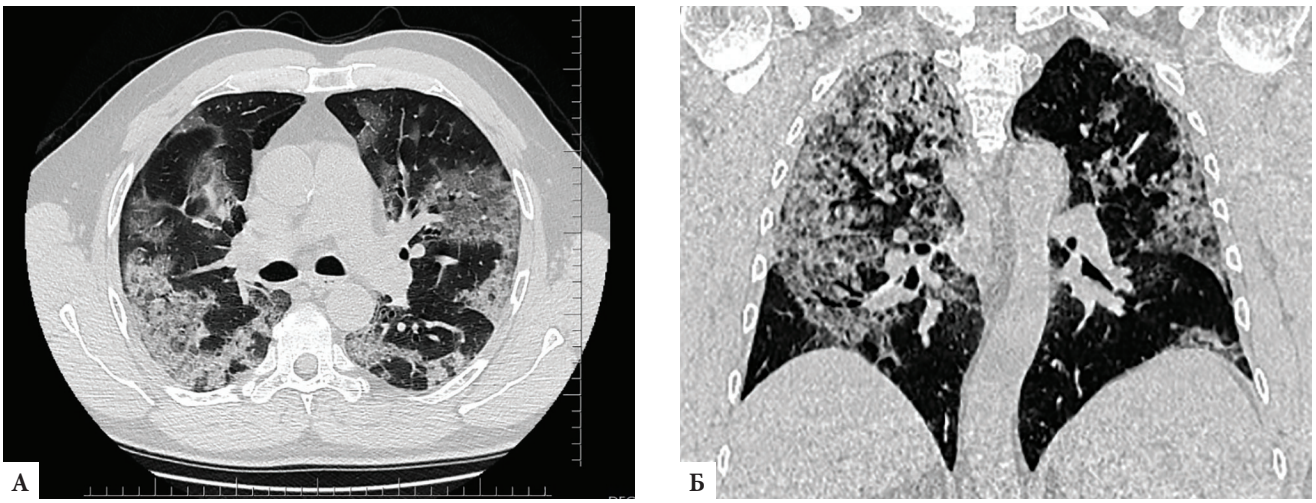


Figure 1 А, Б. *А — axial projection, Б — frontal projection. CT scan of the lungs of a patient with COVID-19 viral pneumonia*

Today, the gold standard for the diagnosis of COVID-19 is the polymerase chain reaction (PCR) for the detection of viral RNA with reverse transcription in real-time. Computed tomography (CT) data in patients with primary false-negative PCR results if COVID-19 is suspected, are an essential component of differential diagnosis [11, 12] (Fig. 1).

Case report № 1

Patient D. 67 years old; referred to N. N. Burdenko National Medical Research Center for Neurosurgery (N.N. Burdenko NMITsN) in May 2020 with complaints of a clear liquid discharge from the nose on the right when the head is tilted.

Past medical history: Hypertension stage II, grade 2, risk of cardiovascular complications, left ventricular myocardial hypertrophy. Chronic hyperplastic gastritis. Heart failure II FC, mitral regurgitation grade II-III, aortic regurgitation grade I-II, tricuspid regurgitation grade II, pulmonary hypertension grade II, diastolic dysfunction of the left ventricular myocardium degree I. The patient did not violate self-isolation restrictions, and had not been in contact with infectious patients. There were no COVID-19 cases in the family.

Medical history: According to the patient, about six months ago, he noted drip outflow of fluid from the nose when the head was tilted. After a month, the nasal discharge intensified. He was treated at the place of residence with a diagnosis of allergic rhinitis without effect. In June, he noted an episode of fever, 38-39 degrees, headaches. He was examined at the place of residence with suspected meningitis. Amoxicillin was empirically prescribed, with no beneficial effect. Magnetic resonance imaging identified a volumetric hypervascular formation of the chiasmatic-sellar region with infrasellar spread measuring 20 × 33 × 22 mm with sphenoid bone destruction. The meningitis diagnosis was not confirmed. The patient was referred to N.N. Burdenko NMITsN to determine the further therapeutic approach.

Neurological examination during the follow-up examination at the Neurosurgery Center identified no abnormalities. PCR identified no virus (SARS-CoV-2) RNA. Coronavirus antibodies (IgG, IgM) were also negative. Computed tomography of thoracic organs was performed. It identified infiltrative changes in the lower lobes of the lungs on both sides. Ground-glass opacity areas were seen on the right, in the lower segments. Calcifications were identified in the 6th segment of the right lung. The roots of the lungs were not dilated. No fluid in the pleural cavity was found. No diaphragm changes. The mediastinum was not displaced.

Complete blood count: white blood cell count is 4.35 10*9/l, neutrophils 72.4%, immature granulocytes 1.1%, lymphocytes 0.85 10*9/l. C-reactive protein was less than 5 mg/ml. The patient had a negative PCR test for coronavirus.

Given the chronic nature of CSF rhinorrhea, CT changes in the lungs may be due to the ingress of cerebrospinal fluid into the lungs. However, given the low lymphocytes in the blood, these changes are highly likely associated with SARS-CoV-2 viral pneumonia. It was decided to postpone the surgery by 10-14 days in order to assess CT changes over time and take repeated tests for coronavirus (swabs from the throat and nose, blood tests for IgM and IgG), followed by a decision regarding the patient's hospitalization at the Neurosurgery Center.

The patient was examined by an Infectious Disease physician at the place of residence. Laboratory tests for

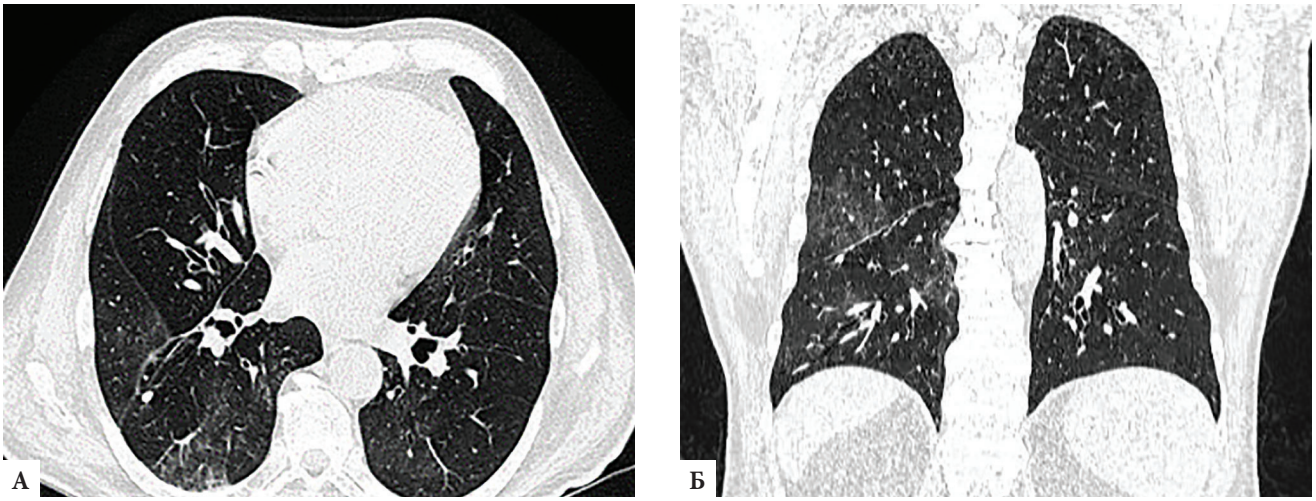


Figure 2 А, Б. *А — axial projection, Б — frontal projection. CT of the first patient's lungs before surgery. Multiple frosted glass areas are noted*

COVID-19, found no SARS-CoV-2 RNA and IgM and IgG antibodies to SARS-CoV-2.

A repeated CT scan of the lungs was performed 16 days later; it showed multiple focal infiltrative changes without changes compared with the previous examination (Fig. 2А, Б).

Repeated sampling and exam of biomaterial was carried out: SARS-CoV-2 viral RNA was not detected.

In view of such inconclusive data, a consultation was held with the chief physician, epidemiologist, therapist, anesthesiologist and neurosurgeons. Since no data were obtained for coronavirus (negative tests for coronavirus, no antibodies), the changes in the lungs were interpreted as a consequence of constant aspiration of cerebrospinal fluid. The patient was admitted to a separate ward. The diagnosis was made: Complex skull base defect in the sphenoid sinus area. Spontaneous CSF rhinorrhea on the right. Aspiration pneumonitis.

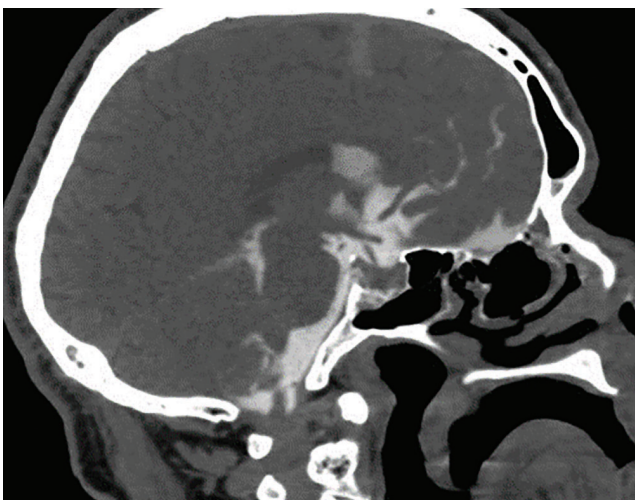


Figure 3. *CT cisternography. Frontal projection. Defect in the area of the Turkish saddle*

Before the surgery, CT cisternography was performed, which showed a defect in the base of the skull in the sella turcica area (Fig. 3).

Treatment progress:

The patient underwent surgery for "Endoscopic endonasal transphenoidal removal of an endosellar pituitary tumor, plastic closure of two CSF fistulas in the area of the sella turcica and posterior cells of the ethmoid bone on the right with auto- and allomaterials".

The postoperative period was satisfactory. Somatic and neurological status in the postsurgical period had no negative changes. In the early postsurgical period, there were no signs of CSF rhinorrhea. The patient was discharged from the hospital on the 9th day after the surgery.

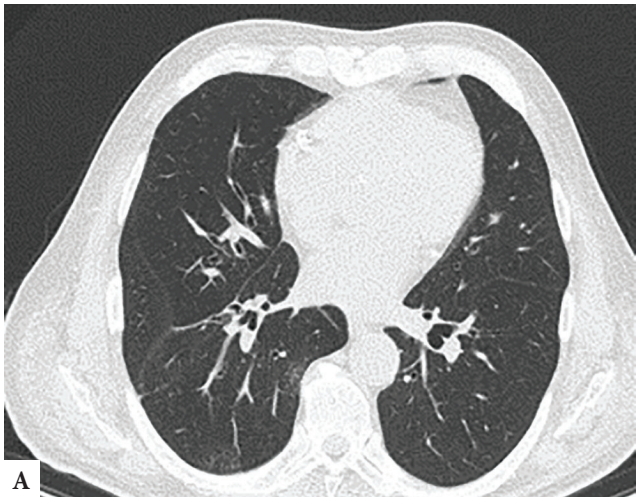
The histological report confirmed the diagnosis of pituitary adenoma.

One month after the surgery, the patient underwent follow-up CT of the chest: the signs of lung damage regressed completely (Fig. 4).

Case report № 2

Patient F., 40 years old, examined at N.N. Burdenko NMITsN for recurrent CSF rhinorrhea.

Medical history. The patient considers himself ill since August 2019, when a liquid discharge from the left side of the nose began for no apparent reason. He visited an otorhinolaryngologist at his place of residence, and was diagnosed with spontaneous CSF rhinorrhea. He underwent treatment in the center, where he underwent surgery for "Endoscopic endonasal plasty of the



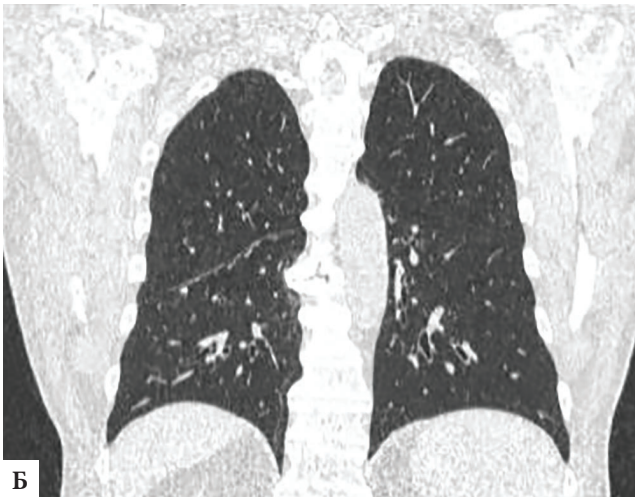


Figure 4 А, Б. *А — axial projection, Б — frontal projection. CT of the lungs one month after surgery*

skull base defect in the area of the lateral recess of the sphenoid sinus on the right". After the surgery he felt well, there was no leak. However, three months after the surgery, he noted a transparent discharge from the nose on the right when the head was tilted. He noted a cough at night and headaches. He visited N.N. Burdenko NMITsN with these signs for repeated surgical treatment. The otorhinolaryngologist's examination showed: Profuse CSF rhinorrhea. Defect in the area of the lateral recess of the sphenoid sinus on the right (Fig. 5).

Past medical history: Traumatic brain injury (TBI) 20 years ago, epilepsy. Degree I obesity.

During examination for hospitalization, the patient was twice tested for SARS-CoV-2 by PCR — no coronavirus RNA was detected. The computed tomography of the thoracic organs showed a pattern of infiltrative changes in the lower lobes of the lungs. No coronavirus antibodies were found. Clinical blood count and biochemical assay were normal. The patient showed no signs of intoxication. No enlargement of peripheral lymph nodes.

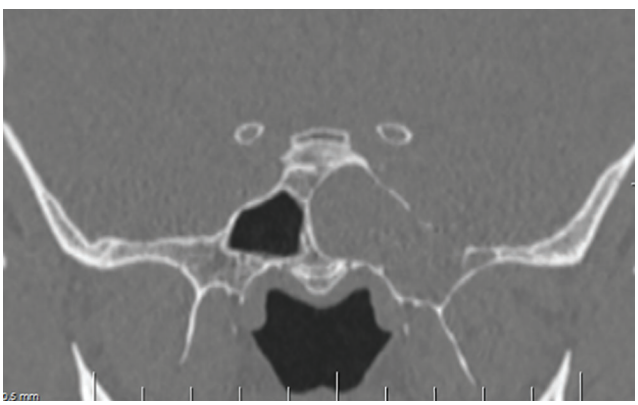


Figure 5. *CT of the brain, frontal projection. Defect of the skull base in the area of the lateral pocket of the sphenoid sinus on the left*

A consultation was held with the chief physician, epidemiologist, anesthesiologist, therapist, neurosurgeons, otorhinolaryngologists. Taking into account the profuse nature of liquorrhea, the inflammatory changes on CT were regarded as a consequence of aspiration pneumonitis due to the leak of cerebrospinal fluid into the lungs (Fig. 6).

Due to the lack of laboratory data for coronavirus (negative tests for coronavirus, lack of antibodies) and the absence of contraindications for anesthesia and surgical treatment, the patient was admitted to the hospital into a separate ward.

Treatment progress:

The patient underwent surgery for "Endoscopic endonasal plasty of the skull base defect in the area of the lateral pocket of the sphenoid sinus using autografts".

The postoperative period was satisfactory. Somatic and neurological status in the postsurgical period had no negative changes. In the early postsurgical period, there were no signs of CSF rhinorrhea. The patient was discharged for outpatient supervision on the 5th day after the surgery.

In the late postsurgical period (one month after the operation), signs of pneumonia according to the CT scan of thoracic organs had completely regressed. Antibodies to SARS-CoV-2 were not detected (Fig. 7).

Discussion

Aspiration is defined as the accidental ingress of oropharyngeal or gastric contents or fluid and particulate matter into the lower respiratory tract. The clinical response to aspiration depends on the nature of the aspirated material, microbiocenosis of the respiratory mucosa and colonization by pathogenic microflora [13, 14].

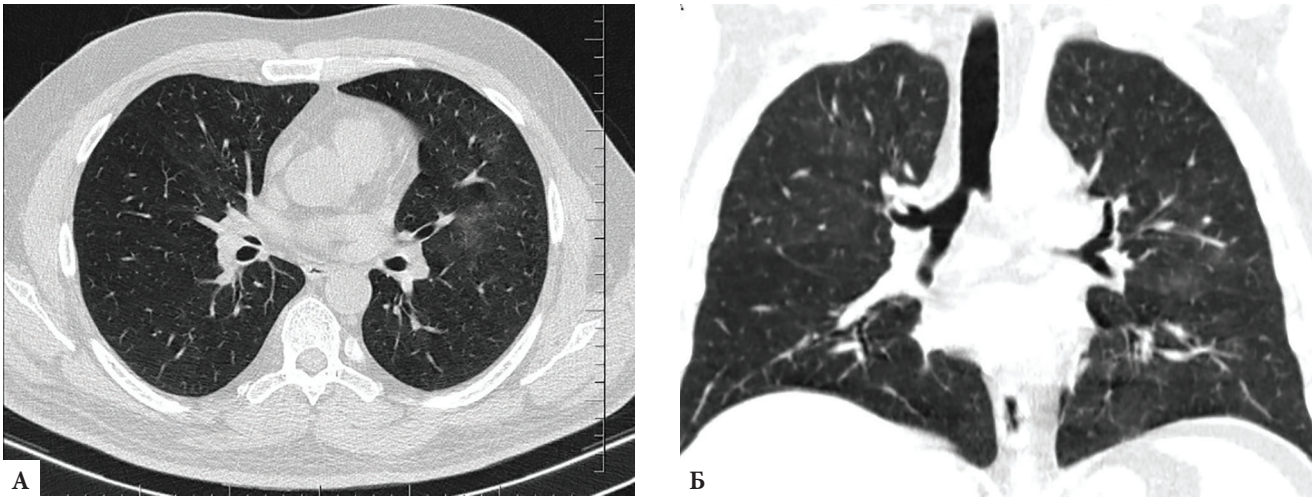


Figure 6 А, Б. *А — axial projection, Б — frontal projection of CT of the chest organs before surgery. There are multiple areas of frosted glass darkening in the left lung*

With profuse CSF rhinorrhea, cerebrospinal fluid may enter the bronchi, which can cause irritation in the respiratory tract. Although patients with skull base defects often complain of cough in the supine position, the literature has very few cases of pneumonitis as a complication of CSF rhinorrhea [15]. In 2016, Justin Seltzer et al. [16] published the first paper devoted to this condition. Until then, this complication was cited in the analysis of series of CSF rhinorrhea treatment cases. However, the diagnostic signs and methods of treatment of aspiration pneumonitis were not described. This is probably because this complication of CSF rhinorrhea was previously underestimated in clinical practice. However, it has acquired particular relevance in the context of the SARS-CoV-2 pandemic.

According to the etiology, CSF rhinorrhea can be spontaneous and traumatic [17]. Traumatic CSF rhinorrhea is associated with traumatic brain injury, and in 80% of cases, it ceases within the first two weeks. Also, traumatic liquorrhea includes liquorrhea arising from various surgical procedures [18]. In spontaneous CSF rhinorrhea, pathogenesis is associated with many factors, such as high body mass index (BMI), intracranial hypertension, empty sella syndrome, and arachnoid granulation [20]. Our patients were overweight. Also, the second patient showed signs of arachnoid granulations on CT. Obesity is accompanied with a decrease in the level of growth hormone, which leads to an increase in leptin secretion, which in turn induces osteopenia. Patients with metabolic syndrome also have a high level of cortisol, testosterone, and norepinephrine. These endocrine changes result in impaired calcium homeostasis, osteoblast function and, ultimately, bone demineralization and the development of osteoporosis, accompanied with skull base bones destruction [21].

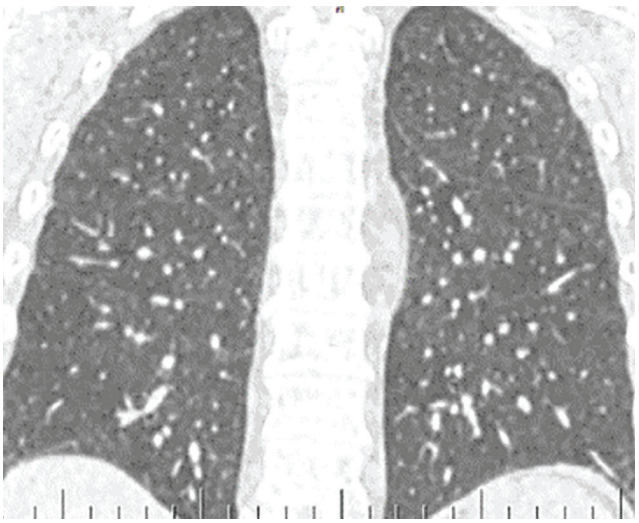


Figure 7. *CT of the lungs one month after surgery, frontal view*

Obesity directly affects the physiology of respiration by increasing the mass and reducing the compliance of the chest walls with the deposition of fat around the ribs, which significantly complicates inhalation. Fat deposition in the mediastinum also limits the lung mobility. With excessive fat deposition in the abdominal cavity, diaphragm dysfunction develops, which is expressed in the disproportion of the ratio between the length and tension of muscle fibers due to their overstretching, which limits the excursion of the diaphragm [22, 23]. All these factors decrease lung volume, especially the expiratory reserve volume (ERV) and functional reserve capacity, which play an important role in maintaining the patency of the distal airways. Therefore, the risk of aspiration pneumonitis in patients with spontaneous liquorrhea is significantly higher than in patients with traumatic liquorrhea [24].

Lung X-ray is used to diagnose pneumonitis. In this case, there is a characteristic localization in the posterior segments of the upper lobes and the upper segments of the lower lobes [25].

COVID-19-induced changes in the lungs are quite variable. However, most authors agree that the most frequent, and at the same time, the most characteristic changes are the "ground-glass" parenchyma compactions (single or multiple), as well as a combination of these changes with consolidation and/or with reticular changes (cobblestone changes) [26]. Most often, pneumonia data manifest on CT as bilateral changes with predominantly subpleural localization in the absence of pleural effusion. In this case, the dorsal arrangement of changes with the involvement of several lobes of the lungs, mainly the lower lobes, is the most typical. In our case, the patient had a ground-glass symptom. However, this symptom is not pathognomonic, but is an indicator of lung tissue density and is a sign of the interstitial nature of infiltration. "Ground glass" is represented by a certain area in which there is a moderately reduced respiratory tissue airiness. The causal factor for this phenomenon is the thickening of the interalveolar septa, as well as the partial filling of the alveoli with contents [27, 28].

According to the literature, no special treatment of pneumonitis with CSF rhinorrhea is required. The symptoms quickly regress after the successful closure of the CSF fistula [29]. Maya Or et al. in 2020 published a paper on aspiration pneumonitis in CSF rhinorrhea [30]. In their series of cases, respiratory symptoms were identified in 6 out of 20 patients with CSF rhinorrhea. The authors report that after the skull base defect plasty, the respiratory symptoms completely regressed without antibacterial treatment.

The Neurosurgery Center continued to provide high-tech medical care to patients at high risk of COVID-19. To reduce and prevent the intrahospital spread of infection among patients, an algorithm was developed. It takes into account data from the epidemiological history, close contact with COVID-19 patients, laboratory data (PCR for SARS-CoV-2 virus RNA) and prehospitalization lung CT data (Table 1).

Table 1. *Algorithm for making a decision on hospitalization of patients*

№	RNA	CT	Epidanamnesis	Clinic	Decision
1.	**NOT detected** RNA SARS-CoV-2 by PCR method with a prescription of material sampling 48 hours before hospitalization	There are no data for viral pneumonia on the CT scan of the chest organs 7 days before hospitalization	There is no contact with patients with COVID-19 for 14 days before hospitalization	There are no clinical signs of the disease	**Hospitalization possible**
2.	SARS-CoV-2 RNA was NOT detected by PCR method with a prescription of material 48 hours before hospitalization	There is evidence for viral pneumonia on the CT scan of the chest organs with a prescription of 7 days before hospitalization	History of transferred COVID-19, there is the presence of IgG antibodies in the blood	There are no clinical signs of the disease	Hospitalization postponed In the future, hospitalization is possible with two negative tests for SARS-CoV-2 by PCR with an interval of 1 day and positive dynamics on the CT scan of the chest organs after 10 days.
3.	SARS-CoV-2 RNA was NOT detected by PCR method with a prescription of material 48 hours before hospitalization	There is evidence for viral pneumonia on the CT scan of the chest organs with a prescription of 7 days before hospitalization	There are no indications of postponed COVID-19 in the anamnesis	There are no clinical signs of the disease	Hospitalization postponed and the patient is sent for observation to a medical organization at the place of residence with a recommendation to perform a test for antibodies of class M and G and repeat the CT scan of the chest organs in dynamics for 10 days.
4.	Detected RNA SARS-CoV-2 by PCR with a prescription of material sampling 48 hours before hospitalization	There are no data for viral pneumonia on the CT scan of the chest organs 7 days before hospitalization	There are no indications of postponed COVID-19 in the anamnesis	There are no clinical signs of the disease	Hospitalization postponed and the patient is sent for observation to a medical organization at the place of residence with a recommendation to undergo a full examination for COVID-19. Further hospitalization is possible no earlier than 4-5 weeks in the absence of a clinical picture and two negative tests for SARS-CoV-2 by PCR with an interval of 1 day and repeated CT scan of the chest organs.
5.	A test for SARS-COV-2 by PCR has been passed, the result will be ready the next day	There are no data for viral pneumonia on the CT scan of the chest organs 7 days before hospitalization	There are no indications of postponed COVID-19 in the anamnesis	The patient is in a serious or extremely serious condition due to the underlying disease.	The patient can be hospitalized in a separate ward of the department, strictly isolated with an accompanying person until the test result is obtained. Upon receiving a positive test for SARS-CoV-2, the patient is transferred to a specialized hospital for the treatment of COVID-19

In the case of CSF rhinorrhea, chest CT may detect aspiration pneumonitis. In this case, the PCR for coronavirus is advisably performed at least twice. If both tests are negative and there are no clinical symptoms of COVID-19 and no contraindications for general anesthesia and surgical intervention, the patient may be hospitalized in a separate ward for plastic closure of the skull base defect.

Conclusions

The changes in the lungs in patients with CSF rhinorrhea are the result of cerebrospinal fluid aspiration. In this case, the changes can be manifested by a short-term focal ground-glass opacity pattern due to the partial filling of the alveoli with fluid without any clinical signs.

In such cases, patients should undergo PCR for detection of SARS-CoV-2 virus RNA at least twice and computed tomography of the chest. If signs of ground-glass opacity are detected, it is recommended to postpone the surgery by 10–14 days in order to assess these changes in computed tomography in real-time and re-test for coronavirus to exclude the viral nature of lung damage.

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