

COVID-19 ASSOCIATED CAVERNOUS SINUS THROMBOSIS: 2-YEAR FOLLOW-UP EXPERIENCE

**Erkin N. Bilalov¹, Okilkhon I. Oripov², Ravshan Z. Umarov³,
Gulomboy U. Khudaibergenov⁴, Bakhodir E. Bilalov⁵**

1 Doctor of Medical Sciences, Professor of the Department of Ophthalmology,
Tashkent Medical Academy, Uzbekistan

2 PhD, assistant of the Department of Ophthalmology,
Tashkent Medical Academy, Uzbekistan

3 assistant of the Department of Otorhinolaryngology, Center for the Development of
Professional Qualifications of Medical Workers, Uzbekistan

4 researcher of the Department of Pathological Anatomy of the
Tashkent Medical Academy, Uzbekistan

5 PhD, assistant of the Department of Ophthalmology,
Tashkent Medical Academy, Uzbekistan

ABSTRACT

This article presents the experience gained over the past 2 years of the coronavirus infection pandemic in monitoring patients with COVID-19 associated cavernous sinus thrombosis. The article describes the results of studies and observations of domestic specialists who worked with these patients. The first descriptions of clinical cases of COVID-19 associated cavernous sinus thrombosis in Uzbekistan and their specific features are given. The results of a comparative analysis of the clinical course of this pathology with classical archival cases of cavernous sinus thrombosis are discussed. The main factors that are associated with the development of complications in patients with coronavirus infection and their frequency of occurrence are listed. Separately, the results of studies by domestic authors devoted to the development of optimal methods for early diagnosis are presented.

Key words: COVID-19; cavernous sinus thrombosis; clinical features; predisposing factors; early diagnosis.

INTRODUCTION

During the pandemic period, domestic scientists also conducted a number of scientific papers devoted to the study of ophthalmological manifestations of coronavirus infection, as well as published descriptions of clinical cases of COVID-19 associated cavernous sinus thrombosis. The most severe ophthalmic complication of coronavirus infection should be recognized as developing in patients with cavernous sinus thrombosis (CST). Despite the fact that this complication is associated with impaired blood circulation in one of the cerebral sinuses, its development leads to damage directly to the optic nerve and cranial nerves responsible for the innervation of the oculomotor muscles. Observations have shown that TCS associated with COVID-19 is characterized not only by a high incidence of irreversible blindness, but also by a high level of mortality, and therefore this complication and the features of its course require a deeper study. In connection with the above, the presence of a sufficiently large sample of cases that have already been registered in our Republic is a prerequisite for a deeper and more comprehensive study of the ophthalmological aspects of COVID-19 associated CST and the development of special clinical guidelines for early diagnosis, treatment and prevention of patients [1,3,7].

General information. CST is a rather rare pathology and there are no publications in the literature devoted to the analysis of a large sample of cases. Observations of patients showed that CST had a "variegated" clinical picture and a severe course with a high mortality rate, which distinguishes it from the classical forms of this complication. It was revealed that in CST associated with coronavirus infection, a more pronounced purulent-necrotic process develops in the nasal cavity, paranasal sinuses and orbit, which was accompanied by a more frequent transition of the inflammatory process to the frontal lobes of the brain with the development of frontal encephalitis or abscess with severe neurological symptoms. Ophthalmic manifestations of CST were persistent and in almost 100% of cases, even with a favorable outcome, the patient developed disability due to the loss of the functional ability of the organ of vision [4,6].

An analysis of the world literature to date shows that fairly large studies involving a large sample of patients were mainly done in India, which in the spring of 2021 faced a severe second wave of the pandemic, during which there was a huge surge in the incidence of cavernous sinus thrombosis associated with COVID-19. It should be clarified that the Indian medical community has combined cavernous sinus thrombosis, along with other purulent-necrotic complications of the maxillofacial, orbital and cerebral region associated with coronavirus infection, into one group - COVID-19 associated mucormycosis. This was due to the fact that in most cases, according to the results of relevant studies, a fungal infection,

mucormycosis, was recognized as the main etiopathogenetic factor in the development of these complications [13,14].

It should be noted that the basis for the development of CST in COVID-19 remains unclear. Since at present only general predisposing factors for the development of thrombosis in coronavirus infection in the form of systemic coagulopathy and vasculitis have been sufficiently studied. At the same time, it remains unclear what, in addition to the anatomical features of the sinus itself and the veins of the maxillofacial region, is a specific local factor that contributes to the development of CST.

First cases and specifics. The first cases of cavernous sinus thrombosis associated with COVID-19 were recorded in our country in July 2020 at the height of the first wave of the pandemic. At that time, only a few reports on the development of thrombosis of the cerebral sinuses in the form of descriptions of clinical cases could be found in the literature, and we can safely say that a significant increase in this complication was one of the first recorded in our Republic [1].

The first cases of COVID-19 associated CST were noted in July 2020 during the first wave of coronavirus infection in Uzbekistan. At the beginning, they had the character of isolated cases and developed in elderly and senile patients with a severe somatic status. From May to August 2020, the TMA multidisciplinary clinic functioned as an anti-covid hospital. During this period, 4 cases of CST were recorded on the territory of the clinic departments. Within 3 months from August to November 2020, after a relative decrease in the incidence of COVID-19, the incidence of CST in patients who had an infection increased significantly, which became a prerequisite for attributing this condition to a complication of coronavirus infection [3,5].

In normal “peaceful” time, as mentioned above, the incidence of CST is extremely low, and therefore, issues related to the process of managing and treating patients have not been fully resolved. In this regard, the sharp increase in cases of CST has raised a number of difficult questions for the medical community. CST by its nature and clinic is a pathology that requires the participation of a number of specialists in the process of managing patients. First of all, this is an ophthalmologist, since the patient himself goes to the doctor precisely because of the development of ocular manifestations (ptosis, loss of vision, exophthalmos). The development of a purulent-necrotic process in the nasal cavity and paranasal sinuses (PNS) required the mandatory participation of an otorhinolaryngologist, and the involvement of the upper jaw and hard palate in the process also attracted the maxillofacial surgeon. The participation of a neurologist

or neurosurgeon is mandatory. The undoubted connection of this kind of complication with coagulopathy also required the intervention of a hematologist. Since most of the patients still had a severe general somatic status, the entire process of patient management was also under the control of the resuscitator. Thus, COVID-19 associated CST is in all respects a complex problem and includes various aspects. At the same time, the role of an ophthalmologist in the process of introducing a patient cannot be limited only to confirming the diagnosis and describing ophthalmological symptoms, since in most cases a full set of narrow specialists could not participate in the work of patients. As a result, some issues related to conservative treatment had to be solved by the ophthalmologist himself [1,2,11].

In scientific sources, there is evidence that thrombosis of the cavernous sinus can occur in various clinical forms, depending on the topography of the lesion of various parts of the sinus. The clinical form of CST, in which there is a partial lesion of certain of its departments, is described in the literature as Jefferson's syndrome. It involves involvement of different parts of the cavernous sinus, which is why it is also called the anterior, middle, and posterior cavernous sinus syndrome.

An analysis of the prevalence of various clinical forms of COVID-19 associated CST showed that in most cases (72.5%) there was a complete cavernous sinus syndrome with damage to all oculomotor nerves, 1 and 2 branches of the trigeminal nerve. Anterior cavernous sinus syndrome occurred in 6.8% of cases, middle cavernous sinus syndrome in 7.8% of cases, and posterior cavernous sinus syndrome in 12.7% of cases [3,4,8].

To study the clinical features of COVID-19 associated CST, a comparative analysis of clinical manifestations in patients of the main sample with clinical manifestations of the classic variant of CST in patients from the archival material of the TMA Multidisciplinary Clinic (2005-2019) was carried out.

First of all, it should be noted that the analysis of archival material revealed only 20 confirmed cases of CST over 14 years. The study showed that in the group with the classic variant of TCS cases, the prevalence of type 2 diabetes was only 30%. An analysis of a series of cases recorded before the pandemic showed that in all cases the development of CST was preceded by a chronic inflammatory process in the oral cavity or paranasal sinuses; among the studied patients, such cases occurred only in 49% [8,10,11].

As is known, in the CST clinic, 2 variants of its course are distinguished, proceeding according to certain patterns: aseptic (ischemic), proceeding slowly with a gradual increase in symptoms, and septic, proceeding acutely with a rapid

increase in severe symptoms. An analysis of classic cases from the archive showed that in 70% of cases there was a septic variant and in 30% an aseptic variant, in which the type of flow could be clearly differentiated by the clinic. An analysis of the symptoms and patterns of their development in a series of cases of COVID-19 associated CST showed that the clinical course cannot be attributed to one of the options.

In the main sample of patients a purulent-inflammatory process developed with a transition to the necrotic stage. However, it was not possible to determine which pathological process was primary in this case due to the simultaneous development of many symptoms. Attention is drawn to the greater severity of symptoms of periorbital cellulitis, decreased sensitivity of the cornea and retinal edema. In cases from archival material, by the frequency of occurrence of ophthalmological signs, it can be judged that the majority of patients had a classic CST clinic [5,6,9].

Thus, the analyzed cases of CST had a specific clinical course. According to the peculiarities of the dynamics of development and the timing of the development of pathognomonic signs, thrombosis of the cavernous sinus cannot be clearly attributed to the aseptic and septic form. On the one hand, in these cases, there was a gradual increase in symptoms, which is typical for the aseptic variant of the course, which is also supported by the patient's coagulogram data. On the other hand, the opening of the orbit showed signs of orbital phlegmon, which could lead to the development of septic thrombosis of the cavernous sinus. However, it is difficult to determine what was primary in this case: the development of purulent hemisinusitis with the transition of the process to the orbit, or the development of thrombosis of the cavernous sinus, followed by the addition of a purulent-necrotic process in the sinuses [2].

Predisposing factors. The analysis of clinical cases showed that in 50.9% ($p < 0.05$) of patients, the development of clinical symptoms of CST was noted within 10 days after discharge from the anti-covid hospital or the end of special anti-covid treatment at home or other medical institution. This period in most cases was characterized by a complete cessation of the introduction of direct anticoagulants or the replacement of their parenteral administration with oral administration. In a relatively smaller proportion of patients (31.3%), the development of symptoms was observed within 10-20 days after the end of anti-covid therapy. At the same time, the analysis showed that only 17.6% of patients developed symptoms during their stay in the hospital.

In most patients, the ELISA results showed the presence of Ig G in the blood (64.7%) ($p < 0.05$), which indicates that this condition is precisely a complication of

COVID-19, since it develops far from being acute stage of the disease. Only in 10.8% of patients, the results of ELISA revealed the presence of Ig M, while the association of Ig M and Ig G was determined in 24.5% of patients [2,5].

To assess the dependence of the development of CST on the severity of the course of COVID-19, an analysis was also made of the frequency of the severity of COVID-19 associated pneumonia depending on the damage to the lung tissue according to CT data. In more than 90% of patients, the disease proceeded with damage to the lung tissue, confirmed by CT. At the same time, damage to 50% of the lung tissue (grade 1-2) was observed in 49% of patients, while 42.1% had damage to more than 50% of the lung tissue (grade 3-4). Only 8.9% of patients did not detect lung tissue lesions on CT.

The most revealing were the data on the presence of hyperglycemia in patients, which, according to the analysis, was detected in 100% of cases. At the same time, it is noteworthy that in 75.5% of patients, hyperglycemia was associated with a history of type 2 diabetes, and in the remaining 24.5%, hyperglycemia was due to prolonged use of corticosteroids or it developed against the background of the infection itself. The basis of the latter phenomenon has not yet been studied, however, the term “COVID-19 associated hyperglycemia” can already be found in the literature [4,6,9].

Most often, patients had long-term therapy with corticosteroids - more than 7 days. At present, according to world standards, the duration of taking corticosteroids by patients, even with the development of severe forms of pneumonia, should be limited to 5 or 7 days. It is noteworthy that 96.1% of all patients received previous anticoagulant therapy. At the same time, the form, scheme and dose of anticoagulant therapy varied.

The analysis showed that 80.4% of patients received long-term humidified oxygen using various devices. At the same time, it was found that 36.5% of patients received oxygen using an oxygen concentrator and the classic Bobrov device (connected to an oxygen cylinder). 27% of patients received oxygen using a CPAP (Constant positive airway pressure) machine. At the same time, it was found that the duration of stay of patients with CST under artificial oxygenation ranged from 7 to 24 days.

Thus, an analysis of the general clinical parameters of patients showed that the development of associated CST in patients with COVID-19 was most often associated with the following factors: the appearance of Ig G in the blood, SARS Cov-2, hyperglycemia, GCS therapy for more than 7 days, prior to irrational anticoagulant therapy and long-term use of humidified oxygen supplies [1,5,9].

Difficulties in early diagnosis and problem solving. Due to its complex neurovascular anatomical relationships, CST is the most serious of all intracranial thromboses. The cavernous sinus is paired and is located at the base of the skull along the lateral surfaces of the Turkish saddle. As a rule, the diagnosis is confirmed on the basis of specific ophthalmic symptoms in the form of ptosis, exophthalmos, ophthalmoplegia, eyelid skin sensitivity loss, etc. However, the diagnosis at the time of the development of these symptoms may be too late in terms of starting effective therapy. This is due to the fact that the development of these symptoms indicates damage to the oculomotor nerves, which is most often irreversible in cases of cavernous sinus thrombosis associated with COVID-19 [3,5,8].

Due to the fact that on the basis of conventional imaging methods it is not always possible to reliably establish the presence of a thrombus, and when contrasting, an uneven distribution of the substance is possible, which can lead to an incorrect interpretation of the results of the study, a more detailed imaging method was proposed, which includes only the study of the cavernous sinus, but also the ophthalmic veins and the cavity of the orbit. The method consists in using special sequences T2 TSE and Dark fluid T2 with thin sections - 0.6-1.6mm [12].

3D thin sections with significant T2 enhancement may allow visualization of individual cranial nerves in the cavernous sinus and adjacent cisternae of the brain. TSE and the special Dark fluid sequence in T2 MRI are standard tools for imaging the orbits and optic nerves. As a rule, the following set of standard parameters is used in the study: TR - 9000 ms, TE - 105 ms, TI - 2500 ms, FOV - 230 mm, matrix 210 x 256, deflection angle - 180°, slice thickness - 3 mm, number of slices – 12, scanning time – 4 min 39 s. The essence of the proposed method lies in the fact that the slice thickness was significantly changed, which made it possible to increase the resolution when visualizing intraorbital structures. A study in this mode allows you to clearly identify the presence of a thrombus in the cavity of the ophthalmic vein, infiltrate in the cavity of the orbit and edema in the optic nerve [8,12].

Studies have shown that the use of this imaging module made it possible to determine the development of thrombosis in the projection of the ophthalmic vein before its transition to the cavernous sinus in 14 patients who underwent COVID-19 and were admitted with complaints of difficulty in nasal breathing, purulent discharge from the nose, and severe headache. The detection of thrombus formation at this stage and the initiation of early intensive conservative therapy made it possible to achieve a favorable clinical outcome in the patient in the form of preserving the eyeball as an organ and partially preserving its functional ability.

Thus, it can be concluded that the proposed MRI imaging method (in TSE and Dark fluid T2 (0.6-1.0 mm) modes) is more effective for the early diagnosis of this complication, since these signs develop much earlier than lesions of bone structures, for visualization which MSCT is more preferable.

Conclusion. Thus, observation of patients during the pandemic showed that COVID-19 associated cavernous sinus thrombosis differs from the classical forms of this complication by more pronounced clinical polymorphism and the development of an extensive purulent-necrotic process in the maxillofacial region. The development of COVID-19 associated cavernous sinus thrombosis was associated with the following factors: the appearance of Ig G in the blood (SARS Cov-2), hyperglycemia, glucocorticosteroid therapy for more than 7 days, prior irrational anticoagulant therapy, and prolonged use of humidified oxygen supplies.

REFERENCES

1. Oripov O.I., Bilalov E.N., Israilov R.I., Umarov R.Z., Bilalov B.E., Khudaibergenov G.U. Pathomorphological features of the necrotic orbital wall lesions and orbital soft-tissue lesions in COVID-19-associated cavernous sinus thrombosis: a case report. // J.ophthalmol.(Ukraine). – 2022. – 5. – P. 71-74. <http://doi.org/10.31288/oftalmolzh202257174>
2. Kasymova M.S., Iminova M.M. Dysfunctional lacrimal syndrome against the background of COVID-19 as an indicator of the severity of ischemia of the organ of vision // Vestnik oftal'mologii. – 2022. - 138(3). – C. 60–64. <https://doi.org/10.17116/oftalma202213803160>
3. Ravshan Z. Umarov, Shukhrat A. Boymuradov et al. Radiographic and Clinical Analysis of Cranio-Maxillofacial Complications of Cavernous Sinus Thrombosis Among 256 COVID-19 Patients // J Craniofac Surg. - 2022 Jul-Aug. - 33(5). – P. 1549-1553. <https://doi.org/10.1097/SCS.00000000000008680>
4. Oripov O.I., Bilalov E.N. COVID-19-associated cavernous sinus thrombosis: a case report // Journal of Ophthalmology (Ukraine) – 2021 – Number 2 (499). – P. 69-71. <http://doi.org/10.31288/oftalmolzh202126971>
5. Ravshan Z. Umarov, Shukhrat A. Boymuradov et al. Aspects of maxillar osteomyelitis in patients who had COVID-19 in Uzbekistan // Advances in Oral and Maxillofacial Surgery. – 2021. – 3. <https://doi.org/10.1016/j.adoms.2021.100106>
6. Munira S. Kasimova, Mufazzalkhon M. Iminova Changes in the organ of vision with a delta strain of coronavirus infection // Chin J Ind Hyg Occup Dis. – 2022. – 13. - P. 48-53. <https://doi.org/10.5281/zenodo.5895268>

7. Oripov O.I., Bilalov E.N., Umarov R.Z. Method of endoscopic decompression of the orbit and optic nerve in case of cavernous sinus thrombosis // *Sovremennye tehnologii v oftal'mologii*. – 2022. - №3(43). – С. 78-82. <https://doi.org/10.25276/2312-4911-2022-3-78-82>

8. Oripov O.I., Umarov R.Z. Method for Early Imaging of COVID-19 Associated Cavernous Sinus Thrombosis // *Sovremennye tehnologii v oftal'mologii* - 2021 – №2(37) – S. 190-192. <https://doi.org/10.25276/2312-4911-2021-2-190-192>

9. Oripov O.I., Bilalov E.N., Israilov R.I., Umarov R.Z., Hudajbergenov G.U., Bilalov B.Je. Hikmatullaev B.H. Pathological characteristics of the features of necrotic lesions of the orbit and the eyeball in COVID-19 associated cavernous sinus thrombosis. case from practice // *Vestnik Tashkentskoj medicinskoj akademii* – 2022 – №6 – С. 183-187. <https://ttaa.tma.uz/vestnik-pdf/2022/ttaa-2022-6.pdf>

10. Kasymova M.S., Iminova M.M. Frequency of ophthalmic complications in COVID-19 infection // *Problemy biologii i mediciny* – 2021 – №2(127) – С. 261-265. <http://pbim.uz/web/upload/1637826757.pdf>

11. Oripov O.I., Umarov R.Z., Bilalov E.N. Etiopathogenesis and clinical manifestation of cavernous sinus thrombosis // *Problemy biologii i mediciny* – 2021 – №2(127) – С. 277-282. <http://pbim.uz/web/upload/1637827162.pdf>

12. Oripov O.I., Bilalov E.N., Umarov R.Z. Radiation Imaging in COVID-19 Associated Cavernous Sinus Thrombosis // *Zhurnal stomatologii i kraniofacial'nyh issledovanij* – 2021 – №1. – S. 80-84. <https://doi.org/10.25739/2181-0966-2021-1-80-84>

13. Honavar S.G. Code Mucor: Guidelines for the Diagnosis, Staging and Management of Rhino-Orbito-Cerebral Mucormycosis in the Setting of COVID-19. // *Indian J Ophthalmol*. – 2021. - 69(6). – P. 1361-1365. doi: 10.4103/ijo.IJO_1165_21. PMID: 34011699

14. Mehta S., Pandey A. Rhino-orbital mucormycosis associated with COVID-19. // *Cureus*. – 2020. – 12. – P. 107-126.