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CAVERNOUS SINUS THROMBOSIS ASSOCIATED WITH COVID-19

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Abstract

COVID-19 associated coagulopathy is the cause of many thrombotic complications in coronavirus infection. One of the possible ophthalmic complications of COVID-19 may be cavernous sinus thrombosis. Cavernous sinus thrombosis associated with COVID-19 has a number of specific features of the clinical course and is due to both the development of coagulopathy and pathological changes in the vascular walls.

Received: August 12, 2021 / Revised: September 08, 2021 / Accepted: September 30, 2021 / Published: October 10, 2021

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Hereby we study the case series of cavernous sinus thrombosis associated with COVID-19 and determine the basis of their development and disease course after coronavirus infection.

12 patients with cavernous sinus thrombosis were under observation. All patients had the history of a previously confirmed diagnosis of COVID-19 and its specific treatment. All patients underwent a comprehensive examination with the inclusion of consultations of related specialists, imaging methods, laboratory tests and pathomorphological study. 6 archive cases of cavernous sinus thrombosis not associated with COVID-19 were studied as control group.

The analyzed cases of cavernous sinus thrombosis had a specific clinical course. According to the characteristics of the dynamics of development and the timing of the development of pathognomonic signs, they cannot be clearly attributed to the aseptic or septic form. In study group, most of the patients showed a significant increase in the level of fibrinogen up to 5 times. The values of other indicators remained in most cases within the normal range or slightly increased. In addition to the standard indicators of the coagulogram, the D-dimer level was determined, which showed a 3-4-fold increase. Pathomorphological study shown a stagnation and sludge phenomenon of erythrocytes with a thinning of the wall in venous vessels.

Analysis of case series of cavernous sinus thrombosis showed that based on the data of clinical, laboratory and morphological studies, it can be concluded that the development of such dangerous complication may be connected with COVID-19 associated coagulopathy.

Keywords: COVID-19 associated coagulopathy; ophthalmic symptoms; cavernous sinus thrombosis (CST); D-dimers;

抽象的

COVID-19 相关凝血病是冠状病毒感染中许多血栓并发症的原因。COVID-19 可能的眼科并发症之一可能是海绵窦血栓形成。与 COVID-19 相关的海绵窦血栓形成具有许多临床过程的特定特征，并且是由于凝血病的发展和血管壁的病理变化。

在此，我们研究了与 COVID-19 相关的海绵窦血栓形成病例系列，并确定了冠状病毒感染后其发展和病程的基础。

观察海绵窦血栓12例。所有患者都有先前确诊的 COVID-19 及其特定治疗的病史。所有患者均接受了包括相关专家会诊、影像学检查、实验室检查和病理形态学研究在内的综合检查。

6 例与 COVID-19 无关的海绵窦血栓形成档案病例作为对照组进行研究。

所分析的海绵窦血栓形成病例具有特定的临床病程。根据发展动力学的特点和病征发展的时间，它们不能明确归于无菌或脓毒症形式。在研究组中，大多数患者的纤维蛋白原水平显著增加了 5 倍。其他指标的数值大多保持在正常范围内或略有上升。除了凝血图的标准指标外

· 还测定了D-二聚体水平，显示增加了3-4倍。病理形态学研究显示红细胞停滞和淤积现象，静脉血管壁变薄。

海绵窦血栓病例系列分析表明，根据临床、实验室和形态学研究数据，可以得出结论，这种危险并发症的发展可能与 COVID-19 相关的凝血病有关。

关键词：COVID-19 相关凝血病；眼科症状；海绵窦血栓形成 (CST); D-二聚体；

Introduction

COVID-19 is a viral disease caused by the SARS-CoV-2 coronavirus. As a rule, severe cases of this disease are characterized by persistent fever, acute lung lesion with acute respiratory distress syndrome, multiple organ failure and high mortality [1,2]. As soon as the first cases of COVID-19 were described, it became clear that the symptoms associated with SARS-CoV-2 are not limited to the respiratory tract and the virus can cause multiple systemic inflammatory reactions and coagulopathy. Various thromboembolic complications have been continuously reported in patients from different countries, regardless of racial origin [3-8].

Close monitoring of COVID-19 patients has shown that many of them had coagulation disorders that resemble other systemic coagulopathies, such as disseminated intravascular coagulation and thrombotic microangiopathy [9-12]. In addition, it turned out that COVID-19-associated coagulopathy also has features that distinguish it from these pathological conditions. Another very important discovery in patients with severe COVID-19 is the tendency to thromboembolic complications in the venous and arterial systems [13,14].

The most common form of pathology of the cerebral venous system, accompanied by the involvement of the visual pathway in the process, is cavernous sinus thrombosis (CST). As a rule, this pathological condition develops due to

infection of the oral cavity, nose, maxillary and frontal sinuses, soft tissues of the face and septic processes in the body, weakened by chronic diseases (immunodeficiency, diabetes mellitus, tuberculosis, hepatitis) [15,16,17]. According to various authors, CST occurs in 0.3–0.5% of cases among all inflammatory diseases [18].

Research objective is to analyze case series of cavernous sinus thrombosis associated with COVID-19 and determine the basis of their development and disease course after coronavirus infection.

Material And Research Methods

A comprehensive study and observation of 12 patients with CST was conducted who underwent treatment at the Multidisciplinary Clinic of the Tashkent Medical Academy in the period from July to October 2020. Patients age ranged from 45 to 72 years, including 7 men and 5 women. All patients had the history of a previously confirmed diagnosis of COVID-19 and data on its specific treatment.

All patients underwent a comprehensive examination with the inclusion of clinical (consultations of related specialists: ENT, ophthalmologist, neurosurgeon, maxillofacial surgeon, infectious disease specialist), instrumental (computed tomography (CT), magnetic resonance imaging (MRI), angiography), laboratory (coagulogram with determination of D-dimers level) and

pathomorphological (histological examination of the material of deceased patients) methods.

For the comparative analysis of the features of the clinical course, we studied and analyzed 6 cases of CST as a control group. Previously these patients underwent treatment courses in the clinic in the period from 2014 to 2019 before the onset of coronavirus infection.

Results

Statistical analysis of data on patient admissions to the clinic from May to October 2020 showed that in total, 5186 confirmed cases of COVID-19 were registered in the clinic during the indicated period of time. Among these cases, complications in the form of CST amounted to 0.23%, which is significantly higher than the average incidence of this pathology in the general population, which is 0.002% [18].

General characteristics of clinical cases. The analysis of patient history revealed that in 2 (16.6%) patients, symptoms developed during hospitalization and receiving specific treatment; in 5 patients (41.7%) symptoms appeared after the end of inpatient treatment; in 5 (41.7%) patients, symptoms developed after treatment at home. The diagnosis of COVID-19 in 66.7% of cases was confirmed by ELISA. Analysis of ELISA results showed that 1 (8.3%) patient had IgM increase for SARS-CoV-2, while 5 (41.7%) patients had IgG increase for SARS-CoV-2; the increase in both fractions was observed in 2 patients (16.6%). Specific signs of COVID-19 associated interstitial pneumonia were found in 11 (91.7%) patients on CT. The majority of patients had a volume of lung tissue lesions equal to 25-50%) (tab. 1).

Table 1.

Main characteristics of COVID-19 course in patients with CST.

Parameter	n (%)
<i>Positive result of ELISA test</i>	8 (66,7%)
Ig M (+)	1 (8,3%)
Ig G (+)	5 (41,7%)
Ig M (+) и Ig G (+)	2 (16,6%)
<i>Lungs involvement</i>	
The absence of <i>lungs involvement</i>	1 (8,3%)
to 25%	2 (16,6%)
25-50%	8 (66,7%)
more than 50%	1 (8,3%)
<i>COVID-19 confirmation</i> Serological test / CT data	66,7% / 91,7%
<i>Previous anticoagulant therapy</i>	7 (58,3%)
<i>Dynamic control of D-dimer level during specific therapy for COVID-19</i>	1 (8,3%)

As mentioned above, only 7 of 12 patients received treatment in a hospital setting, which included anticoagulant therapy. 5 patients received outpatient treatment at home for various reasons. It should be noted that among the patients who received inpatient treatment, only 1 had a dynamic control of D-dimer level during therapy, in other cases its determination was not carried out and the control was limited to the determination of the main indicators of the coagulogram in the form of hematocrit, fibrinogen, reference test, activated partial thromboplastin time (APTT), international normalized ratio (INR) and prothrombin index (PTI).

Features of the CST course in the surveyed patients. First of all, it should be noted that the analysis of archival material revealed only 6 confirmed cases of CST over 4 years. The study of case series showed that 10 (83.3%) of 12 patients in the core group suffered from type 2 diabetes in the stage of decompensation for many years, while in the control group this indicator

was 4 (66.7%) of 6 patients. Analysis of the case series recorded before the pandemic revealed 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 in only half (tab.2).

Table 2.
Comparative analysis of COVID-19 associated cases of CST and classic cases of CST.

Parameter	Study group (n=12)	Control group (n=6)
COVID-19	+	-
DM	10 (83,3%)	4 (66,7%)
Presence of chronic inflammatory process in oral cavity or paranasal sinuses.	6 (50%)	6 (100%)
Clinical form of CST	It cannot be attributed exactly to one of the clinical forms	Aseptic form (16,7%) Septic form (83,3%)
One side / Both side	9 (75%) / 3 (25%)	2 (33,3%) / 4 (66,7%)
Development of CST after purulent hemi sinusitis	It is not possible to determine exactly what was primary	5 (83,3%)
Headache	10 (83,3%)	6 (100%)
Ophthalmic symptoms		
<i>Ptosis</i>	9 (75%)	6 (100%)
<i>Esophthalmus</i>	7 (58,3)	5 (83,3%)
<i>Ophthalmoplegia</i>	11 (91,7%)	6 (100%)
<i>Periorbital cellulitis</i>	12 (100%)	4 (66,7%)
<i>Chemosis</i>	12 (100%)	3 (50%)
<i>Decreased corneal sensitivity</i>	11 (91,7%)	5 (83,3%)
<i>Decreased sensitivity of the skin of the paraorbital area</i>	9 (75%)	5 (83,3%)
<i>Optic disc edema</i>	12 (100%)	6 (100%)
	10 (83,3%)	4 (66,7%)

<i>Retinal edema</i>		
Coagulogram indices on the background of TCS	+++	++
Fibrinogen	=	+
APTT	=	+
INR	+	+
PTI	++++	-
D-dimers		
(+) - degree of increase		
(=) - within normal limits		
(-) - not determined		
General lethality	7 (58,3%)	4 (66,7%)
With surgical intervention	3 (25%)	
With conservative treatment	4 (33,3%)	4 (66,7%)

CST has 2 forms of disease course, proceeding according to certain patterns: aseptic (ischemic), proceeding slowly with a gradual increase in symptoms, and septic, proceeding acutely with a rapid increase in pronounced symptoms. The analysis of classic cases from the archive showed that in 83.3% there was a septic variant and in 16.7% the aseptic variant, in which the type of course could be clearly differentiated according to the disease pattern. Analysis of symptoms and patterns of their development in case series of COVID-19 associated CST showed that the clinical course cannot be attributed to one of the options.

In 5 cases of the control group, the development of CST was accompanied by purulent hemi sinusitis, affecting the maxillary, ethmoid, or frontal sinuses. In case series of the core group, we observed the purulent-inflammatory process in the paranasal sinuses (PNS) (Fig. 1). However, it was not possible to determine which pathological process in this case was primary due to the simultaneous development of many symptoms.

The incidence of ophthalmic manifestations of CST is presented in the Tab. 2. Noteworthy is the high severity of symptoms of periorbital cellulite (Fig. 2), decreased sensitivity of the cornea and congestive retinal edema. In the cases of the control group, according to the incidence of ophthalmological signs, it can be assumed that the most of patients had a classical CST clinic.

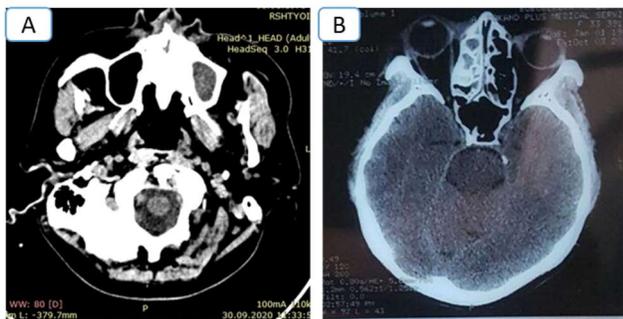


Figure 2. CT scans. A. On axial section, signs of left-sided hemi sinusitis are determined (the presence of contents in the cavity of the maxillary and ethmoid sinuses in density (35-45) close to pus). B. On axial section, signs of right-sided hemi sinusitis are determined, possible presence of pus in orbit with exophthalmos.



Figure 1. Appearance of patients with TCS. Ptosis, edema and hyperemia of the eyelids (signs of periorbital cellulitis), conjunctival chemosis, exophthalmos and mydriasis are determined.

Analysis of changes in the coagulogram indicators showed that in the cases of the control group there was a slight increase in the main coagulogram indicators such as fibrinogen, PTI, APTT and INR. In cases of the study group, most of the patients showed a significant increase in the level of fibrinogen up to 5 times. The values of other indicators remained in most cases within the normal range or slightly increased. In addition to the standard indicators of the coagulogram, the D-dimer level was determined, which showed a 3-4-fold increase. It should be noted that dynamic control of the D-dimer level during therapy was carried out only in 2 cases. The D-dimer level during the period of receiving anticoagulants in the acute phase of COVID-19 in these cases was not significantly increased.

The tactics of managing patients in the core group had differences due to the general condition of the patients. In the cases of the control group, most of the patients received conservative therapy, including anticoagulants, anti-inflammatory and antibacterial drugs. The mortality rate in the group was 66.7%. In the core group, many patients underwent surgical interventions in various modifications in order to decompress the cavities. In other cases, conservative therapy was carried out with the above groups of drugs. Analysis of the mortality rate showed that the overall mortality in the considered cases of COVID-19 was 58.3%. At the same time, among these patients, 3 were

operated on, and 4 received only conservative treatment.

2 patients had a development of acute disorders of cerebral circulation of the type of hemorrhagic stroke. Moreover, in one case, the development of a stroke preceded the development of CST and was accompanied by the development of encephalitis of the frontal lobes, followed by the development of abscess and hemorrhage. In one case, hemorrhagic stroke was the direct cause of death. During the autopsy of the patient died of the stroke, the pathological material (vessels from the brain) was taken in order to study the morphological bases of thrombosis in them. The conclusion of the pathomorphological examination of the cerebral vessels is presented below.

Pathomorphological study of the material showed that in some vessels there was a lesion of the endothelium with rejection and exposure of the basement membrane. The figure presents the marginal arrangement of blood elements in the vessel in the form of adhesion and infiltration of the wall with leukocytes and lymphoid cells (Fig. 3). In small vessels of the brain, the formation of fibrin filaments in the vessel and the formation of a special mesh was noted, which closed the cavity of the vessel in the form of a segmental closure. In the venous vessels of the brain, there was a stagnation and sludge phenomenon of erythrocytes with a thinning of the wall and pronounced perivascular edema of the brain tissues. Coronavirus infection contributed to the development of coagulopathy in the vessels of the brain in the form of thrombus formation (in the cavity of the fibrin-platelet arteries, in the veins of the erythrocyte, in the capillaries of the hyaline thrombus). Coagulopathy and thrombus

formation in vessels of different calibers were the cause of edema, encephalomalacia and perivascular cerebral infarction development.

Discussion

Regarding the clinical features of COVID-19 associated coagulopathy, many reports on thrombotic conditions can be found in the literature [5-9]. In the recent study, COVID-19 patients reported a high rate of thromboembolic complications (7.7% of the total; 21% cumulative) despite the use of anticoagulant therapy within 24 hours of admission. Such complications included mainly venous thromboembolism (57%) and episodes of arterial thromboembolism in the form of ischemic stroke and acute coronary syndrome (43%) [6].

The recent analysis by the group of researchers [8] showed that the incidence of thromboembolic complications in patients with COVID-19 with acute respiratory distress syndrome was much higher (11.7%) than in the control group of archived cases who did not have COVID-19, despite the ongoing anticoagulant therapy. The thrombotic risk associated with COVID-19 has been further confirmed by early autopsy reports that demonstrate microvascular thrombosis as well as severe inflammatory changes in their wall.

The analyzed cases of CST had a specific clinical course. According to the characteristics of the dynamics of development and the timing of the development of pathognomonic signs, CST cannot be clearly attributed to the aseptic and septic form [18,19,20]. On the one hand, in these cases, there was a gradual increase in symptoms, which is characteristic for the aseptic course, which is also supported by the patient's coagulogram data. On the other hand, opening

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 hemi sinusitis 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.

Despite the ambiguity of the issue on the primary pathophysiological relationship, it is obvious that the developed state is associated with the past coronavirus infection. The increased level of D-dimers in these patients indicates the development of COVID-19 associated coagulopathy, which could become the main factor leading to the development of this condition.

Based on the pathological study, it can be concluded that with coronavirus infection in the vessels of the brain, almost all parts of the vascular system are affected. Initially, the endothelium is affected in the vessels, due to viremia and toxemia, the surface of the endothelium is damaged, in which dystrophic swelling of the cytoplasm develops, followed by rejection and exposure of the basement membrane. Subsequently, the basal and elastic membrane, the muscle layer and the adventitia of the vascular wall are affected. Thrombus formation occurs due to damage to the endothelium.

Based on the study, we may conclude that the cases of CST identified in a sufficiently large number were associated with the fact that the control of anticoagulant therapy in patients was performed by determining standard coagulogram

parameters without determining the D-dimers level. The results of determining their level in patients with developed CST showed that it was high, which positively correlated only with the level of fibrinogen. It is of interest that a similar picture was observed in patients 7-30 days after the end of anticonvulsant therapy as a manifestation of the so-called post-covid syndrome. In this regard, it should be mentioned that even in the long term after the end of anticoagulant therapy in patients with a burdened history (diabetes mellitus, ischemic heart disease, or old age), the coagulogram parameters should be monitored with the determination of the D-dimers level at certain times.

Conclusion

Thus, the study once again proved that COVID-19 is a systemic infection that can affect all systems of human organism. At the same time, the degree and specificity of the coagulation system disorders is still not fully understood. Analysis of case series of cavernous sinus thrombosis showed that based on the data of clinical, laboratory and morphological studies, it can be concluded that the development of such dangerous complication may be associated with COVID-19 associated coagulopathy. The study of case series revealed not only the atypical clinical course of the process, but also specific shifts in the parameters of the blood coagulation system along with changes in the walls of blood vessels at the histological level. But still, the issues on managing such patients and choosing the most optimal treatment tactics remain open.

Authors Contributions

OO, BB and AN performed clinical examinations of patients. LT observed patients during specific therapy for COVID-19. RI

responsible for pathomorphological study of patients. EB devised the study, performed surgery during treatment of patient and contributed to the analysis, discussion and main interpretation of results and writing of the article. AY and SB contributed to the analysis, discussion and main interpretation of results and writing of the article.

Competing Interests

The authors declare no conflict of interest.

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