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CLINICAL STUDY

Radiographic and Clinical Analysis of Cranio-Maxillofacial Complications of Cavernous Sinus Thrombosis Among 256 COVID-19 Patients

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Background: A heavy burden of cranio-maxillofacial complications may be encountered in corona virus disease-2019 patients due to the associated coagulopathy and inflammatory consequences of the disease. This study aims to describe clinical and radiographic features of these complications in 256 patients who developed 1 or more of the following complications: cavernous sinus thrombosis, osteomyelitis or necrosis of the jaws.

Methods: Clinical assessment of cranial nerve function and general clinical assessment were performed. Imaging techniques used were multi-slice computed tomography, magnetic resonance imaging, and MRI with contrast enhancement.

Results: Thromboembolism of brain and facial blood vessels were associated with inflammation and necrosis. Multi-slice computed tomography/MR angiography showed thrombotic occlusions of the internal carotid artery in the area of the cavernous sinus, and in the ophthalmic veins. Cavernous sinus thrombosis was attributed to coagulopathy and, inflammation of the paranasal sinuses, especially sphenoiditis. A noticeable increase in the size of the cavernous sinus was detected. Compression of the cranial nerves in the CS region causes dysfunction and pathology in the corresponding regions.

Key Words: COVID-19, cavernous sinus thrombosis, complication: diagnostics, radiology, MR-angiography

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The severe adverse health outcomes and socioeconomic consequences of corona virus disease-2019 (COVID-19) pandemic are undoubtedly evident, which warrants a timely and effective diagnostic and therapeutic approach. The main outcomes of severe acute respiratory syndrome virus-2 infection encompass various pulmonary and extrapulmonary manifestations. Among these complications the cranio-maxillofacial complications represent a heavy burden of debilitating and irreversible outcomes associated with compromised esthetics and function.[1,2] Several consequences are identified in the form of cavernous sinus thrombosis (CST), osteomyelitis of the jaw, necrotic changes of the facial bones, and visual impairment which develop not only in active COVID-19 patients, but also in those who have recovered.[3]

Perhaps the most severe outcomes are represented by CST. This potentially fatal disorder was associated with approximately 100% mortality rate prior to antibiotics era due to sepsis or central nervous system infection.[4] The anatomic and clinical significance that was described by Duncan and Bright,[5] respectively in the early1800s is attributed to the complex anatomic neurovascular relations making CST the most complicated type of intracranial septic thrombosis.[6] Vital structures that may be adversely affected include cranial nerves III, IV, V1, V2, and VI which travel through the sinus or its lateral wall. Consequently, various adverse outcomes may be encountered such as severe headaches, retro-orbital pain, visual disturbances and ophthalmoplegia. On the other hand, CS drains blood from the facial vein, and the ophthalmic veins into the basilar plexus, and it is closely related to the sphenoid sinus. Therefore, infection, or trauma of the paranasal sinuses or any of the anatomic structures drained by the cavernous sinus, including the mid-face, orbit, pharynx, oral cavity, and ear, may predispose to CST.[7] Prior to the COVID-19 era only 200 cases were reported in literature[8] and approximately 0.2 to 1.6 CST cases per 100,000 were reported yearly[9] with an increased susceptibility in diabetic or immunosuppressed patients,[10] and a strong association with the development of mucormycosis as an invasive and aggressive infection in COVID-19 patients.[11]

There is limited data on the changing trends in epidemiology of CST in the COVID-19 era in terms of prevalence, predisposing factors and adverse outcomes. Therefore, more studies are warranted to suggest the recommended diagnostic methods to prevent this severe complication and mitigate its adverse outcomes especially irreversible and debilitating ones. Moreover, more data on clinical presentation, clinical course and risk factors for the development of severe maxillofacial complications in COVID-19 are much needed at this stage. Within the context of diagnostic methods imaging techniques have been employed for various indications, however, their important role in the detection and description of hard and soft tissue pathology of the face, and skull in COVID-19 patients has not been well-explored.

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Therefore, this study was conducted among a large group of COVID-19 patients who developed CST in association with mucormycosis to describe the clinical and radiographic findings of associated cranio-maxillofacial complications of CST, osteomyelitis/ osteonecrosis of the upper jaw, and pan / sinusitis.

MATERIALS AND METHODS

Patients

Patient group included all patients who had specific cranio-maxillofacial complications of COVID-19 and who were admitted to the interdisciplinary unit of the Tashkent Medical Academy from July 2020 to November 2021. Cranio-maxillofacial complications included CST, osteomyelitis of the upper jaw, and pan / sinusitis. In all patients, COVID-19 was initially confirmed by PCR followed by immune-enzymatic or immunochemiluminescent analysis. All patients were tested for complete blood count, coagulation tests, biochemical, microbiological, and histopathological tests. Excluded patients were those who had non-COVID-19 maxillofacial infectious complications, or pre-existing coagulopathy. Pregnant women and patients unwilling to participate in the study were also excluded.

The study was ethically approved by the ethics committee of Tashkent Medical Academy IRB# (6/1–1444), which was in accordance with Declaration of Helsinki. All patients included in this study have provided their informed consent prior to participation.

Clinical and Radiographic Assessment

Patients were clinically assessed for headache, vomiting, edema of the optic discs, focal/generalized seizures, and progressive depression of consciousness. Assessment also included local neurological symptoms, including dysfunction, for the cranial nerves III, IV, 1st and 2nd branches of the V, VI, and, where indicated the VII cranial nerve bilaterally.

All patients underwent neuroimaging using multi-slice computed tomography (MSCT), magnetic resonance imaging (MRI), and contrast-enhanced magnetic resonance angiography. Magnetic resonance imaging of the CS included routine T2, fluid-attenuated inversion recovery, and precontrast T1- weighted images of the entire brain. The following features were assessed by contrast-enhanced MRI of the brain, size, and contour of the cavernous sinus, coronary views, heterogeneous, and asymmetric filling defects after contrast enhancement, and increased orbital fat density. Vascular assessment was carried out to identify thrombosis, thromboembolism affecting veins and tributaries leading to the cavernous sinus and narrowing/occlusion of the carotid artery. The respective radiological data of 18 healthy people were used for the purpose of comparison. All radiological measurements and assessments were performed by 1 radiologist. Diagnosis of osteomyelitis was confirmed by clinical assessment (mobility of bone structures, teeth, with the release of purulent exudate), MSCT and histopathological analysis of surgical biopsy specimens.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics version 17.0. Descriptives were calculated to obtain mean values (mean ± standard deviation). Statistical tests of significance of differences employed non-parametric tests of: Mann–Whitney and Wilcoxon T test. Where a normal distribution of indicators was encountered, the significant differences in mean values were determined by the Student *t* test. The statistical level of significance was set at $P \leq 0.05$.

RESULTS

Demographic and Clinical Findings

A total of 256 patients were included in this study consisting of 148 male (57.8%) and 108 female (42.2%) patients. The age range was 18 to 76 years, (mean = 52.5 ± 3.9 years). Most patients attended during recovery period of the disease (74%). All patients had existing comorbidities in the form of type II diabetes mellitus (41%), arterial hypertension, coronary heart disease, and morbid obesity. Most CST patients (76%) were hospitalized within 2 months after recovery, while a proportion of 24% of patients had CST in the acute phase of COVID-19 infection. It was noticed that most patients attended during the summer months and peaked in August (Fig. 1).

The earliest and most frequent symptom of thrombosis was a sudden intense headache, which was mostly diffuse (92% of cases) and was poorly controlled by analgesics. The headache was described by patients as unusual in nature and intensity. Other clinical manifestations of vascular disorders include vomiting, edema of the optic nerve discs, "superior orbital fissure" syndrome, and progressive depression of consciousness. Headache or orbital pain was often accompanied by focal neurological deficits, especially the cranial nerves III, IV, V1, V2, VI, and VII to a lesser extent. In more advanced stages of thrombosis, ophthalmopathy was encountered in the form of ophthalmoplegia, ptosis of the upper eyelid with anesthesia of the upper and lower eyelids and unilateral or bilateral paresthesia of the upper 2/3 of the face, and exophthalmos on the side of the affected cavernous sinus. A proportion of 52.8% of patients reported a visual field cut before complete loss of vision. Other pathologies detected in CST patients were in the form of necrosis of the palatal (68%) and nasal (100%) mucosa. Further, a total of 144 patients (56.2%) developed osteomyelitis of the bones of the maxillofacial region on the affected side. A total of 43.8% of CST patients developed chronic osteomyelitis, followed by osteonecrosis of the bones of the upper jaw, forehead, zygomatic bone palate and sinus walls in the affected side [Supplementary Digital Content, Table 1, http://links.lww.com/SCS/E65].

Bilateral CST was detected in 42 (16.4%), and mortality affected 52 (20.3%)

Radiographic Findings

According to MSCT and MRI / MR angiography, it was noted that the differences in the transverse CS diameter, internal carotid artery and superior ophthalmic vein diameters were significantly different when healthy and patient groups were compared ($P \leq 0.05$). A statistically insignificant expansion was noticed in anteroposterior and vertical measurements of the CS compared with the size of the CS in healthy people ($P > 0.05$). Areas of occlusion of the internal carotid artery in the area of the CS, and

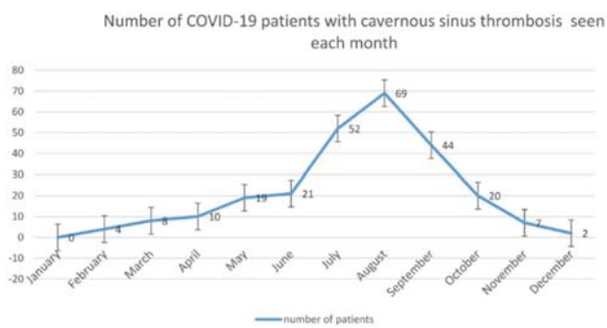
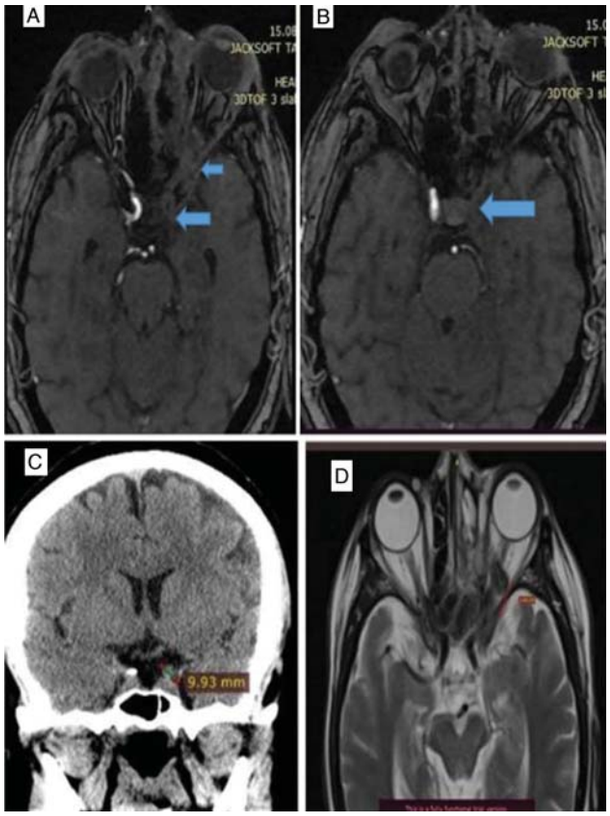


FIGURE 1. Number of new COVID-19 patients with cavernous sinus thrombosis admitted per month to the hospital. COVID-19, corona virus disease-2019.



AQ11 **FIGURE 2.** MRI with contrast: (A) MR angiography, axial projection. Thrombosis in cavernous sinus and orbital vein, and hypertrophy of the oculomotor muscle (B) Axial projection. Partial occlusion of the left internal carotid artery segment of the cavernous sinus zone. (C) Complete occlusion of the right ICA. (D) MRI, axial projection. Thrombus at the level of the orbital vein, exophthalmos I degree, left-sided sinusitis and right-sided sphenoiditis. MRI, magnetic resonance imaging.

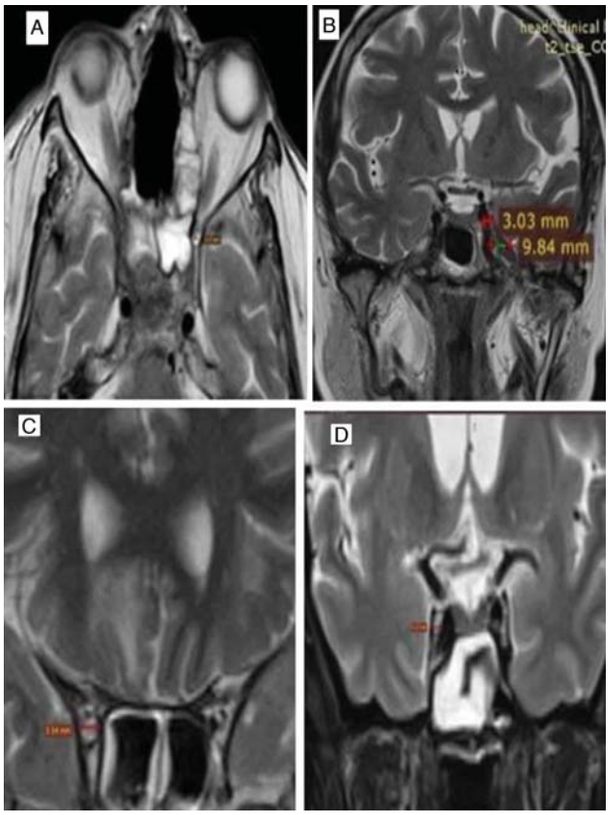


FIGURE 3. MRI, (A) axial projection. Occlusion / thrombus at the level of the superior ophthalmic vein. (B) coronary projection. There is an enlargement of the size of the cavernous sinus on the left. (C, D) coronary projection. Incomplete occlusion of the internal carotid artery in the cavernous sinus, there is hyperplasia of the mucous membrane of the right sphenoid sinus. MRI, magnetic resonance imaging.

ophthalmic vessels were detected of which the average value of the thrombus size was 21.15 ± 1.845 mm. In case of incomplete occlusion of the vessels, a narrowing of the vessel lumen by the thrombotic mass was found (Density $= 46 \pm 4.15$ HU). With complete occlusion, the vessel diameter expanded significantly ($P < 0.001$). Osteonecrosis of the upper jaw was radiographically evident as decreased density, destruction of bones, which were significantly different from healthy group according to MSCT data ($P < 0.05$). [Supplementary Digital Content, Table 2, http://links.lww.com/SCS/E65].

With MRI in standard modes, signs of venous thrombosis can be detected in the form of an increase in the signal intensity from the cavernous sinus, rarely the sigmoid sinuses, the venous sinuses are asymmetric. During MR venosinusography, a decrease in the signal from the blood flow along the affected side, as well as a compensatory increase in the signal from the blood flow, and vasodilation on the opposite side are revealed. Other supporting findings are a ''dirty'' appearance of the retro-orbital fat and enlargement of the extraocular muscles. Figures 2–5 show radiographic features of the cavernous sinus and associated vasculature, eye, and mucous membrane of the sphenoid.

DISCUSSION

Medically compromised patients are a highly vulnerable group to symptomatic COVID-19 and its complications. This group of patients are likely to increase in number with time as the pathogenic mechanisms of COVID-19 and its complications start to unravel. This study is the first study to include a large sample of more than 200 patients of COVID-19 patients who developed mucormycosis followed by thrombotic and necrotic complications in the craniomaxillofacial area. The results of this study clearly highlight the importance of employing several diagnostic investigations and criteria to establish early diagnosis and elicit timely treatment prior to the development of severe or irreversible morbidities. These morbidities were critically debilitating for the affected patients and often lead to fatal outcomes. This study showed that CST could be an immediate complication of COVID-19, and that the medically complex group should be particularly monitored to prevent the gravid complications of this disorder. Diagnosis of CST in COVID-19 patients is established based on specific clinical ophthalmic and neurological symptoms. Approximately 9 in 10 patients with CST presented with a severe type of headache that did not respond to analgesics. With venous sinus thrombosis, venous pressure rises, as a result of which the absorption of cerebrospinal fluid is impaired, and intracranial hypertension develops with subsequent severe type of headache. Other symptoms include ophthalmic symptoms including ptosis, exophthalmos, ophthalmoplegia, and sensory deficit in areas innervated by the ophthalmic and maxillary branches of the trigeminal nerve. Ophthalmic manifestations are often a complication of CST complication COVID-19.[12] These symptoms should represent an alert sign for clinicians to proceed with further

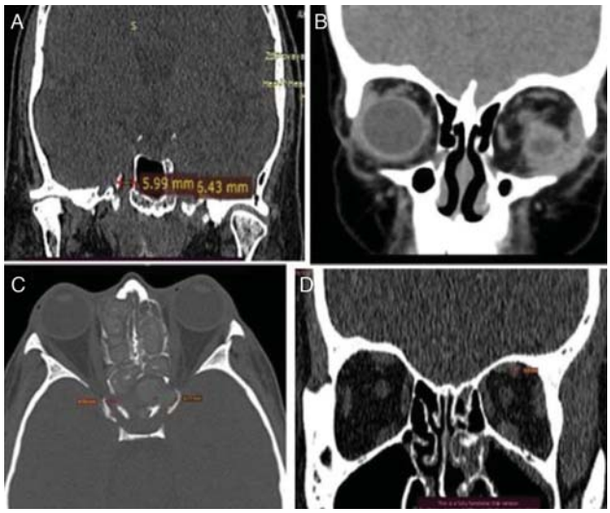


FIGURE 4. MSCT. (A) Coronal projection. Expansion of the left cavernous sinus. (B) MRI. Coronal projection. Endoophthalmitis, exophthalmos on the left. S. MSCT. (C) Axial projection. Pansinusitis, expansion of the cavernous vein on the right. (D) Coronal projection. Dilation / thrombus of the superior ophthalmic vein on the left. MRI, magnetic resonance imaging; MSCT, multi-slice computed tomography.

diagnostic microbiological and radiographic investigations. Successful treatment and improved prognosis are dependent on early detection and accurate diagnosis to prevent the irreversible tissue damage often encountered in cases of CST associated with COVID-19. Further, mortality rate is reduced in CST with aggressive management to 30%.[4] Thromboembolic events after COVID-19infection have been reported mainly in the pulmonary vasculature, however; thromboembolic complications of the nervous system with subsequent cerebrovascular stroke have been increasingly reported.[13]

There is limited information on the diagnosis, clinical presentation, clinical course, and risk factors for the development of severe maxillofacial complications in COVID-19. Various reliable imaging techniques can be employed such as orthopantomography, multispiral computed tomography (CT), and MRI. Clear Indications for performing these imaging techniques have not been well described, and guidelines for radiological examination of COVID-19patients in various phases of treatment have not been developed yet. In modern practice, CT or MRI with contrast have been used to confirm the diagnosis of CST with the latter being more reliable to distinguish it from other possible differential diagnoses such as orbital cellulitis.[14] While MRI identifies important soft and hard tissue changes in the sinuses for example, MR venography characteristically identifies absent blood flow in the affected cavernous sinus, stenosis or occlusion of the intravenous segment of the carotid artery and determine the presence of a thrombus in the lumen of the orbital vein.[15] Therefore, they represent the preferred choice to determine an accurate and timely diagnosis way before the appearance of clinical manifestations that could undermine prognostic success.

Of particular importance is the MSCT which can significantly increase the diagnostic accuracy by measuring the height and width of the bones of the facial skull, jaws, and alveolar ridges.[16] This provides reliable estimation of the densitometric characteristics of the jaw bones, to assess anatomic structures such as the canal morphology, and the mucous membrane lining of the maxillary sinuses. Further, it identifies inflammatory and sequestration changes in osteomyelitis cases.[17] Postoperatively, imaging methods are also essentially applicable to establish the diagnosis of early or late complications.

Although non-contrast MSCT of the head, may not provide initial diagnosis of CST, it can reveal several subtle anomalies, such as engorgement or enlargement of the superior and / or inferior ophthalmic veins, bulging of the lateral edges of the cavernous sinus, exophthalmos, the bony tissues of the maxillofacial regions, and sinusitis as shown by the density of the sinus contents. Since multiple thrombotic events are common in this condition, dural venous sinuses and cerebral veins, cerebral infarctions, meningitis, cerebritis or brain abscess should be examined

Thus, it can be argued that the proposed imaging methods for COVID-19 associated complications are highly sensitive and allow timely diagnosis and initiation of appropriate treatment, which will allow achieving more favorable clinical outcomes. The detection of thrombus formation at this stage and the beginning of early intensive conservative therapy allows achieving a favorable clinical outcome in the patient in the form of preservation of the eyeball, facial bones as an organ and partial preservation of its functional ability. Therefore, this problem requires further comprehensive study.

In Uzbekistan, the peak of the COVID-19 wave occurred in July to August of 2020 and 2021. Consequently, the treatment of patients with CST, osteomyelitis and pansinusitis as a complication of COVID-19 increased proportionally.[18] Warm weather is thought to increase blood clotting and viral coagulopathy leads to cerebral thrombosis in vulnerable individuals with comorbidities.[19] Furthermore, inaccurate diagnosis, and failure to establish the correct differential diagnosis is often associated with delayed treatment and worsened prognosis. Patients may often be incorrectly diagnosed with facial palsy, migraine, simple toothache, odontogenic infections, or peripheral ophthalmologic complaints. Therefore, medical history and interdisciplinary approach are essential for establishing the accurate diagnosis and initiating the most appropriate treatment plan, before encroaching on the irreversible stage of debilitating complications or even mortality. Diagnosis of COVID-19 associated CST is confirmed on the basis of specific ophthalmic and neurological symptoms in the form of ptosis, exophthalmos, ophthalmoplegia, and sensory deficit in areas innervated by CN V1 and V2. With the development of osteomyelitis, poor prognosis is expected as there is less chance in obtaining effective therapy. This is due to the associated nerve damage, which is usually irreversible in cases of COVID-19-associated CST.[20–22]

Imaging methods employed in this study are highly sensitive and they allow timely diagnosis and initiation of appropriate treatment, which will lead to more favorable clinical outcomes.[23]

CONCLUSIONS

It can be concluded that a substantial proportion of medically compromised patients who contract COVID-19, will eventually progress to more serious complications in the cranio-maxillofacial region, if early diagnostic interventions were not established. Several factors influence the severity and variability of outcomes including comorbidities, the degree and location of involvement, and the degree of vascular occlusion. Multi-slice computed tomography and MRI contrast angiography are important imaging techniques in the diagnosis of CST, in order to determine the changes in the cavernous sinus, the state of blood supply and the location of the thrombus in the vessel, the density of the bones of the face, and the paranasal sinuses. In the treatment of thrombosis of the cavernous and other sinuses, it is necessary to restore the blocked vascular permeability, intensify anticoagulation therapy for the purpose of recanalization, and control of the coagulopathy to prevent vision loss, osteonecrosis, and other debilitating complications.

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