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COVID-19-Associated Cerebral Venous Sinus Thrombosis: A Case Report and Review of the Literature

COVID-19 İlişkili Serebral Venöz Sinüs Trombozu: Olgu Sunumu ve Literatür Derlemesi

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Abstract

Coronavirus disease-2019 (COVID-19) is a global health problem causing morbidity and mortality. It has a clinical spectrum ranging from an absence of symptoms to acute respiratory distress syndrome. A new COVID-19-related clinical finding is published daily. We report here a patient with COVID-19 and cerebral venous sinus thrombosis and no deep vein thrombosis or any underlying predisposing factors for hypercoagulation.
Keywords: COVID-19, sinus thrombosis, headache

Öz

Tüm dünyayı etkileyen Koronavirüs hastalığı-2019 (COVID-19), morbidite ve mortaliteye yol açan bir sağlık sorunu olarak karşımıza çıkmaktadır. Koronavirüs hastalığı-2019, asemptomatikten akut solunum sıkıntısı sendromuna kadar değişen klinik spektrumda görülebilir. Her gün COVID-19 ilişkili farklı bir klinik bulgu yayınlanmaktadır. Burada, derin ven trombozu ya da hiperkoagülasyon için altta yatan herhangi bir hazırlayıcı faktörü bulunmayan bir hastada gelişen, COVID-19 hastalığı ve serebral venöz sinüs trombozu olgusu sunulmuştur.
Anahtar Kelimeler: COVID-19, sinüs trombozu, baş ağrısı

Introduction

Coronavirus disease-2019 (COVID-19) is a global health problem causing morbidity and mortality. Our knowledge about this disease is increasing, and therefore, COVID-19 is diagnosed with different clinical presentations. Recently, Dong et al.[1] presented eleven COVID-19 clinical manifestations. Thrombosis, one of the aforementioned manifestations, reflects that COVID-19 is associated with hypercoagulopathy. Although venous and arterial thromboses are increasingly reported in patients with COVID-19, cerebral venous sinus thrombosis (CVST) is rarely reported[2,3]. In this case report, we present a patient with COVID-19-associated CVST and review similar case reports published in PubMed until January 2021.

Case Report

A 34-year-old male patient presented to the emergency room with fever, cough, diarrhea, and nausea. The patient had no history of chronic disease and medication and no contact with COVID-19-infected patients.

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His symptoms started a few days before his presentation. In the emergency room, his vital signs were as follows: body temperature of 39 °C, respiratory rate of 24 breaths/minute, and oxygen-free saturation rate of 91%. His other system examinations were unremarkable. Laboratory results, imaging results, and vital signs of the entire follow-up are shown in Table 1. The naso-oropharyngeal swab taken for COVID-19 was positive. Chest computed tomography (CT) findings were bilateral, multifocal, patchy, ill-defined ground-glass opacities and crazy-paving appearance at peripheral regions predominanty which were accepted as typical findings of COVID-19 pneumonia.

We treated the patient using hydroxychloroquine, azithromycin, favipiravir, and nasal oxygen (Table 1). We added piperacillin-tazobactam for secondary infection. The patient developed severe headache, agitation, and stool incontinence on the second day of treatment. On his neurologic examination, no lateralization was observed. The patient underwent brain magnetic resonance imaging (MRI) and non-contrast MR venography. Sagittal T2-weighted (Figure 1A) and axial fluid-attenuated inversion recovery (Figure 1B) images showed abnormally high signal intensity and absence of flow void in the medial part of the transverse sinus. The coronal maximum intensity projection view from noncontrast two-dimensional time-of-flight MR venography revealed the loss of signal intensity in the medial two-thirds of the left transverse sinus (Figure 1C). The findings were consistent with transverse sinus thrombosis. The patient was hemodynamically stable and had no strong predisposing risk factors for venous thromboembolism. We added enoxaparin sodium 2x6000 IU (60 mg)/0.6 ml to the patient's treatment. On the follow-up, the patient developed cough, tachypnea, and dyspnea and had a saturation rate of 90% despite receiving an oxygen treatment, 5 L/minute; therefore, we admitted him to the intensive care unit (ICU).

On the seventh day of treatment, the patient underwent follow-up chest CT with contrast. The chest CT images revealed bilateral multifocal, multisegmental ground-glass opacities and consolidation, predominantly in the lower lobes and sub pleural regions. We observed no pulmonary thromboembolism (PTE) within the pulmonary arteries and their branches. The patient received tocilizumab 400 mg intravenously, and we added dipyridamole to his treatment (Table 1). Two days after receiving tocilizumab, the patient's general condition improved and his dyspnea and cough rapidly regressed. We transferred him from the ICU to the ward.

Follow-up brain MRI after 10 days showed the disappearance of the high signal intensity on sagittal T2-W images (Figure 1D). Consequently, the thrombus in the left transverse sinus was lost. The patient's general condition improved. We discharged him and added warfarin (5 mg/day on international normalized ratio of 2.0-3.0) to his anticoagulant therapy.

Other Case Reports Published in the Literature

Twelve case reports, including 20 patients with CVST associated with COVID-19, were published in the literature[4-15]. The characteristics of the cases are summarized in Table 2. The ages of the patients were between 17 and 72 years (median: 49), and most of them were males (80%). Although diabetes mellitus, hypertension, and obesity were the most frequent comorbidities, eight patients (40%) had no comorbidities. The most prominent presenting symptoms of CVST were headache, hemiplegia, hemiparesis, aphasia, altered mental status, and focal or generalized seizures. The time from the onset of COVID-19 symptoms to CVST symptoms was between one and fourteen days (median: 7). Coronavirus disease-2019 swab test was positive for all patients, except patient 2. The diagnosis of patient 2 was based on radiological features. All patients had bilateral pulmonary infiltrates, except four patients[7,11,12]. Two patients had PTE[10,14]. In all patients, the imaging findings were consistent with CVST. However, in two patients, the initial CT scan and CT venogram were reported as normal[5,8]. Anticardiolipin antibodies were positive in seven patients[5,9,11,14]; anti-beta 2 glycoprotein antibodies two patients[11,14] and lupus anticoagulant one patient[6]. D-dimer levels were recorded in nine out of the twenty patients and were higher than the normal level in all of them[6-8,11,12]. All patients were treated with anticoagulation therapy (low molecular weight heparin, heparin, or oral anticoagulants), and four patients underwent an endovascular intervention[8,11]. Two patients developed CVST despite administering standard anticoagulation prophylaxis[11]. National Institutes of Health Stroke Scale (NIHSS) scores were reported in nine patients and were between 1 and 31 (median: 14). While 16 patients survived, four patients, aged 72, 38, 41 and 23 years, died[7,8]. In two of the deceased patients, NIHSS scores were 14 and 16[8].

Discussion

Cerebral venous sinus thrombosis is an uncommon subtype of stroke accounting for approximately 0.5-1% of strokes[4,16,17]. It is more common in the younger population. The predisposing risk factors of CVST are genetic predisposition to thrombophilia, connective tissue diseases, oral contraceptive use, malignancy, pregnancy, and local infections of the head and sinuses. However, in some patients, none of the risk factors are detected[18]. In a recent study, patients with CVST developing after vaccination against Severe acute respiratory syndrome-CoV-2 with ChAdOx1 nCoV-19 were reported[19]. No deep vein thrombosis or any underlying predisposing factors were observed in our patient. Additionally, eight of the 20 patients (40%) reviewed in this paper had no comorbidities.

Table 1. Laboratory and imaging results and vital signs of the complete follow-up of the patient

	First admission	On the 2nd day of treatment	On the 4th day of treatment	On the 7th day of treatment/transfer to the intensive care unit	On the 8th day of treatment	On the 18th day of treatment, at the time of discharge
Creatinine, mg/dl	0.69	0.72	0.69	0.48	0.56	0.69
AST, U/L	27	60	304	36	154	48
ALT, U/L	21	33	351	26	307	169
LDH, U/L	247	550	506	375	312	175
CK, U/L	668	594			51	28
Leukocyte, mm^3	2710	3140	2050	2310	2780	3580
Lymphocyte, mm^3	400	310	550	520	810	1080
Hemoglobin, gr/dL	14.9	14,4	14	13.9	14.5	14
Platelets, mm^3	104000	157000	148000	179000	383000	353000
CRP, mg/L	48	115	118	48	12.8	0.7
Procalsitonin, microgr/L	0.18	0.49		0.16		
Ferritin, microgr/L	216	586	703		416	237
Fibrinogen, g/L		3,84	5.63	4.96	5	2.72
D-dimer, mg/L	0.50				0.70	0.35
Respiratory rate, min	24	24	22	20	20	20
Fever, °C	39	37.2	36.7	36.5	36.4	36.5
sO_2, %	91	96	96	98	98	98
Imaging studies	**Chest CT:** typical chest CT findings of COVID-19 pneumonia	**Cranial MR and MR venography:** appearance of high signal intensity and loss of signal void in the medial part of left transverse sinus consistent with venous thrombosis		**Chest CT and angiography:** typical chest CT findings and progression of COVID-19 pneumonia; no pulmonary thromboembolism		**Cranial MR and MR venography: disappearance of high signal intensity in the left transverse sinus**
Treatment	Hydroxychloroquine; favipiravir; piperacillin + tazobactam	Hydroxychloroquine; favipravir; piperacillin + tazobactam; therapeutic enoxaparin sodium	Hydroxychloroquine; favipiravir; piperacillin + tazobactam; therapeutic enoxaparin sodium; dipyridamole	Hydroxychloroquine; piperacillin + tazobactam; therapeutic enoxaparin sodium; dipyridamole	Hydroxychloroquine; piperacillin + tazobactam; therapeutic enoxaparin sodium; dipyridamole; tocilizumab 400 mg	Coumadin

mg/l: Milligram/liter, U/L: Unit/liter, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, CK: Creatinine kinase, CRP: C-reactive protein, IL-6: Interleukin-6, sO_2: Oxygen saturation, CT: Computed tomography, MR: Magnetic resonance, COVID-19: Coronavirus disease-2019

Venous sinus thrombosis is observed three times more frequently in women than men[20]. This higher frequency occurs due to the additional risk factors, such as pregnancy, puerperium, and oral contraceptive use[21]. However, most patients (80%) reported in Table 2 were males. On the other hand, COVID-19 infects men at a higher rate (~60% of patients), and male sex has also been associated with poor prognosis[22].

Cerebral venous sinus thrombosis can present as intracranial hypertension (headache, papilloedema, and visual problems), encephalopathy (mental status change and coma), or focal syndrome (seizures, paresis, and aphasia)[6]. It can also cause cerebral infarction or hemorrhage. Headache is the most common presenting symptom of CVST, followed by seizures and focal neurologic deficits[7]. Of the 20 patients with COVID-19 and CVST, 10 had severe or worsening headache (Table 2). However, headache is a symptom of acute COVID-19, which can make CVST misdiagnosed. Thus, a persistent worsening headache should be investigated in patients with COVID-19, especially in the presence of thrombotic risk factors, even in those with a mild disease[13].

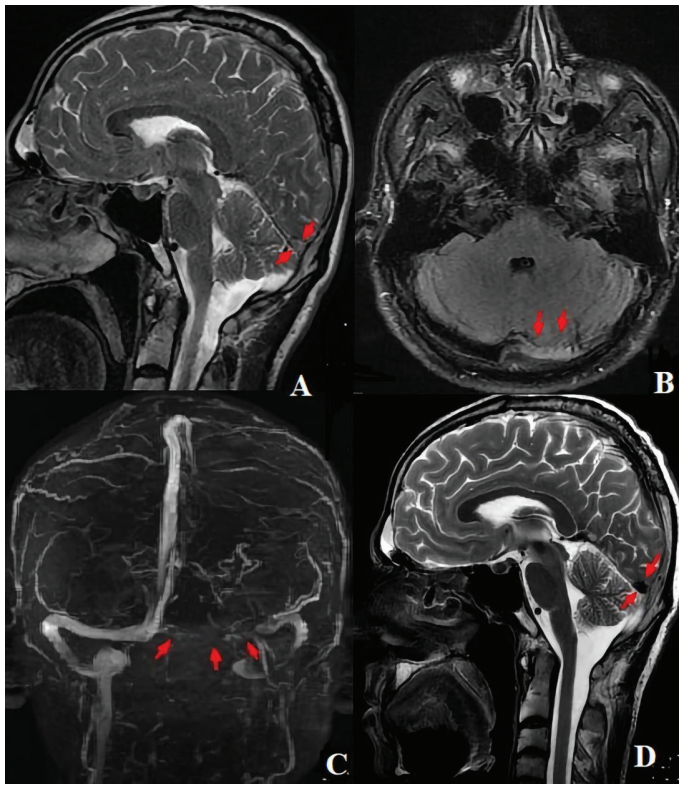

Figure 1. A) (red arrows) Abnormally high signal intensity sagittal T2-weighted. B) (red arrows) Absence of flow void in the medial part of the transverse sinus in axial fluid-attenuated inversion recovery. C) (red arrows) Loss of signal intensity in the medial two-thirds of left transverse sinus in the coronal maximum intensity projection view from noncontrast two-dimensional time-of-flight magnetic resonance venography. D) (red arrows) Disappearance of the high signal intensity on sagittal T2-W images after treatment

The close association of inflammation and thrombosis is well known. Thrombosis may occur due to any severe infection. Coronavirus disease-2019 increases the risk of venous thromboembolism[18]. Although the mechanism of hyper coagulation in COVID-19 is incompletely described, some mechanisms were purposed. The cytokine storm can induce the production of clotting factors or cause an endothelial injury because the virus binds to angiotensin-converting enzyme 2 receptors on the endothelium, which may activate a coagulation cascade[6,7,18]. The severity of inflammation is associated with hyper coagulation. The severe form of the disease and poor results may be associated with this cytokine storm. Interleukin-6 can be accepted as a predictor of mortality in patients with COVID-19[1].

Elevated D-dimer increases blood coagulation and thrombin formation[11]. Thus, high D-dimer level can demonstrate the hypercoagulable state and risk of thrombosis in patients with COVID-19[7]. D-dimer levels were recorded in nine of the 20 patients in Table 2 and were elevated in all of them. While anticardiolipin antibodies were positive in some patients, their role in hypercoagulopathy remains uncertain and may be transient. However, they may help identify patients at a greater risk of CVST[23]. In systematic review and meta-analysis, CVST is more frequently observed after severe COVID-19 infection and in the presence of vascular pathologies[24].

Thrombotic events such as pulmonary embolism, venous thrombosis, and stroke may be the initial symptoms of COVID-19. Three of the 20 patients reviewed in this paper were admitted to the hospital with symptoms of CVST[4,5,12]. The initial symptoms of patients 1, 2, and 16 were persistent severe headache, delirium and generalized seizures, respectively. They had been well previously with no neurological or respiratory symptoms and with no COVID-19 history. On the other hand, patients 4 and 6 had a recent history of COVID-19 infection, but they had no respiratory or systemic symptoms of COVID-19 on admission[7]. They were admitted to the hospital with sudden onset of headache, nausea, emesis, and neurological symptoms.

The initial CT scan or CT venogram was normal in three patients[4,5,8]. Patient 1 was admitted with a right-sided headache and his initial CT venogram was normal. His symptoms improved and he was discharged. However, he was readmitted four days later with acute neurological symptoms with a NIHSS score of 10, and a repeat CT venogram revealed right sigmoid and transverse sinus thrombosis. Patient 2 was admitted with delirium and his initial head CT scan was normal. Due to his persisting problems, a week later, repeated CT scan and CT venogram showed dural venous sinus thrombosis. Patient 8 was admitted with confusion and sudden global aphasia. Her initial CT scan and CT angiography were normal. While waiting for brain MR imaging, she worsened and was intubated. Repeat cranial CT showed venous infarction and intraventricular hemorrhage.

Radiological evaluation aids in early awareness and detection of CVST in patients with COVID-19 who have persistent headache, elevated D-dimer levels, and neurological signs. Early diagnosis using cranial CT and CT or MR venography is important, because prompt anticoagulation therapy or surgical intervention or both may improve the outcome of the disease[2,25]. However, the optimal choice of anticoagulant and treatment duration for CVST is unknown[26]. Interestingly, some patients with COVID-19 developed CVST despite administering the standard anticoagulation prophylaxis[11].

Conclusion

As a result, COVID-19 can be seen with a clinical spectrum ranging from an absence of symptoms to acute respiratory distress syndrome. A new COVID-19-related clinical finding is published daily. We think that COVID-19 will present with a thousand faces. In this article, we wanted to highlight CVST

Table 2. Summary of patients with cerebral venous thrombosis associated with COVID-19

Patient number	Age	Sex	Comorbidity	Presentation of CVST	Imaging findings (CT/MRI)
1[4]	59	M	DM, HT, and obesity	First admission, persistent severe headache; second admission (4 days later), reduced power and numbness in the right upper and lower limbs, slurred speech, and dysphasia	**Initial CT scan:** hyperdensity within the superior sagittal sinus, right transverse sinus, sigmoid sinus, and upper right internal jugular vein. **Initial CT venogram:** normal. **Repeat CT venogram:** filling defect in the right sigmoid and transverse sinus involving the torcula
2[5]	50	M	None	Delirium, persisting problems with executive dysfunction, and dyspraxia	**Initial CT scan:** normal. **Repeat CT scan and CT venogram:** dural venous sinus thrombosis involving the whole of the superior sagittal, left transverse, and left sigmoid sinus down to the level of the jugular foramen. Thrombosis of the vein of Labbé and a small parenchymal hemorrhage within the left temporal lobe
3[6]	63	M	DM, asthma	Left-sided weakness, focal seizures, and subsequent status epilepticus	**CT scan and CT venogram:** extensive venous sinus thrombosis with bilateral venous cortical infarcts and acute cortical hemorrhage
4[7]	17	M	Obesity	New-onset left-sided headaches, occasional emesis and blurred vision, no focal neurologic deficits, and papilledema in fundoscopic exam	**MRI and MR venography:** extensive dural venous sinus thrombosis involving the straight sinus, torcula, left transverse, and sigmoid sinus, extending into the jugular vein, as well as right transverse sinus, superior sagittal sinus, and left vein of Labbe
5[7]	72	M	Breast cancer in remission	Dysarthria and left hand weakness	**CT angiogram:** filling defect in the right transverse sinus and jugular bulb suggestive of venous sinus thrombosis
6[7]	26	M	None	Sudden onset left-sided hemiparesis followed by severe headache, nausea, and dizziness	**CT scan:** hemorrhage in the right parasagittal region. **MR venography:** ho evidence of dural venous sinus thrombosis. **MRI:** ho clear cortical vein thrombosis. **Cerebral angiogram (next day):** a venous anomaly and a filling defect of the right junction of the vein of Trolard with the superior sagittal sinus. **Repeat angiogram (several weeks after discharge):** cortical vein thrombosis, demonstrating a persistent filling defect with substantial improvement in venous drainage, and no evidence of arteriovenous fistula or malformation
7[8]	38	M	Mild autism	Headache and altered mental status	**CT scan:** hyperdensity in the straight sinus, distal superior sagittal sinus, torcular, and right transverse sinus, as well as in several cortical veins adjacent to the superior sagittal sinus consistent with cerebral venous thrombosis and cerebral edema. **CT venography:** consistent with cerebral venous thrombosis, including a near-occlusive thrombus in the right internal cerebral vein
8[8]	41	F	Estrogen-containing oral contraceptives	Confusion, sudden episode of global aphasia, and left-gaze preference	**Initial CT scan:** normal. **Initial CT angiography:** no large-vessel occlusion. **Repeat CT scan:** venous infarction in the left basal ganglia, thalamus, and mesial temporal lobe with hemorrhagic transformation, intraventricular hemorrhage, and obstructive hydrocephalus. **CT venogram:** occlusion of the internal cerebral veins with significantly reduced enhancement of the vein of Galen and distal straight sinus
9[8]	23	M	Diabetic ketoacidosis with new-onset DM	Lethargy, headache, and decreased level of consciousness	**CT scan:** patchy areas of low density in the bilateral cerebral hemispheres with foci of subcortical hemorrhage in the left parieto-occipital region. **CT angiogram:** negative. **MRI:** confluent, nonenhancing regions of pathologically reduced diffusion throughout the subcortical and deep hemispheric white matter bilaterally, left greater than right
10[9]	29	M	Iron deficiency anemia	Tonic clonic seizures with postictal confusion, decreased level of arousal, global aphasia, diplopia, decreased blink to threat on the right, and a mild-to-moderate right facial palsy; on examination, bilateral 6th nerve palsies and bilateral papilledema	**CT scan:** left temporoparietal hemorrhagic venous infarct with edema and mass effect with 5 mm rightward shift, venous thrombosis in distal left transverse and sigmoid sinus. **MRI:** hyperintense DWI signal of the left temporoparietal hemorrhagic infarct with mass effect and effacement of the left lateral and third ventricle with 4 mm rightward shift. **MR venography:** absence of flow in the left transverse and sigmoid sinus and left internal jugular vein secondary to venous thrombosis

11[10]	56	M	None	Severe headache and vomiting	**CT scan and MRI:** compatible with cerebral venous thrombosis from confluences of sinus to left transvers sinus
Patient number	**Age**	**Sex**	**Comorbidity**	**Presentation of CVST**	**Imaging findings (CT/MRI)**
12[11]	51	M	HT, coronary artery disease, and hyperlipidemia	Hemiplegia on the left side	**CT scan:** acute thrombus in the right internal carotid artery (ICA) from its origin and an M1 occlusion **Repeat CT scan (post-stroke day 1):** Large right MCA infarct in temporal, posterior frontal and parietal lobes **CT venogram and CT angiogram:** Right ICA occlusion
13[11]	70	M	None	Acute left hemiparesis and facial droop	**CT scan:** Large right MCA and ACA infarct. **Repeat CT scan (post-stroke day 1):** Hemispheric right MCA stroke with mass effect and right to left herniation. **CT venogram and CT angiogram:** Right M2 occlusion
14[11]	54	M	HT	Headache and progressively worsening mental status into coma	**CT scan:** bilateral thalamic and basal ganglia infarcts with hydrocephalus and cerebral edema. **CT venogram and CT angiogram:** filling defects in the vein of Galen, straight sinus, bilateral internal cerebral veins, and right basal vein of Rosenthal
15[11]	48	M	None	Acute right-sided hemiplegia and aphasia	**CT angiogram:** acute left MCA occlusion. **MRI:** large acute infarct in the left MCA territory, with mass effect and mild petechial hemorrhage
16[12]	30	M	None	Generalized tonic clonic seizures	**CT scan:** small hypodense lesion in the right temporal lobe anteriorly with mild surrounding edema and mass effect. Tiny foci of hyperdense hemorrhage within the lesion and in the adjacent Sylvian fissure. **MRI:** a hematoma and subarachnoid hemorrhage in the Sylvian fissure. **MR venogram:** nonocclusive venous thrombosis of the torcula, left transverse sinus, and sigmoid sinus, extending to occlude the proximal part of the left internal jugular vein
17[13]	18	M	None	Worsening headache	**CT scan:** hyperdense internal cerebral veins. **CT venogram:** filling defects throughout the sigmoid and transverse sinuses bilaterally, extending into straight and superior sagittal sinuses
18[14]	44	F	None	Headache, altered mental status, aphasia, and right hemiparesis	**CT angiography:** contrast medium filling defect (empty delta sign) in the vein of Galen, straight sinus, and the torcular herophili due to dural sinus thrombosis with poor representation of left internal cerebral vein
19[15]	62	F	Morbid obesity	Headache, altered vision, sudden right hemicorporeal deficit, and altered consciousness	**CT scan and MRI:** large confluent intraparenchymal hemorrhage in the left fronto-temporal lobes. **CT venogram:** cerebral venous thrombosis of the left transverse sinus, straight vein, vein of Galen, and internal cerebral veins
20[15]	54	F	Breast cancer in remission	Severe headache	**CT scan and MRI:** large hemorrhagic infarction in the left temporal lobe **CT venogram and MR angiography:** cerebral venous thrombosis of the left transverse sinus

M: Male, F: Female, CVST: Cerebral venous sinus thrombosis, DM: Diabetes mellitus, HT: Hypertension, CT: Computed tomography, MRI: Magnetic resonance (MR) imaging, COVID-19: Coronavirus disease-2019

associated with COVID-19, which is a rare complication of COVID-19.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.A., E.A., A.E., B.Ç.T., O.K., R.G., Concept: A.A., E.A., Design: A.A., E.A., A.E., R.G., Data Collection or Processing: A.A., E.A., Analysis or Interpretation: A.A., E.A., A.E., B.Ç.T., O.K., Literature Search: A.A., E.A., Writing: A.A., E.A.

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