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The Incidence of Cerebral Sinus Venous Thrombosis in Patients Diagnosed with Pseudotumor Cerebri During the COVID-19 Pandemic

COVID-19 Pandemisi Döneminde Psödotümör Serebri Tanısı Alan Hastalarda Serebral Sinüs Venöz Tromboz İnsidansı

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ABSTRACT Objective: To emphasize the increasing frequency of cerebral sinus venous thrombosis (CSVT) among the causes of pseudotumor cerebri (PTC) and the necessity of investigating it in patients presenting with papilledema during the COVID-19 pandemic. **Material and Methods:** Complete ophthalmological examinations, magnetic resonance imaging (MRI) and contrast-enhanced magnetic resonance venography (MRV) data of 44 patients diagnosed with PTC in a tertiary neuro-ophthalmology clinic, from the beginning of the COVID-19 pandemic to the present were recorded. Patients without documented increases in intracranial pressure by lumbar puncture, patients with abnormalities in cerebrospinal fluid (CSF) biochemistry and microbiology analysis, and patients with intracranial mass, obstructive hydrocephalus, or meningitis on MRI were excluded. **Results:** MRI and contrast-enhanced MRV imaging were evaluated together in 36 of the 44 patients with COVID-19 positivity. The mean age of the included patients was 36.9 years (minimum: 9-maximum: 63). Among these 36 patients who underwent combined imaging, 14 (38.8%) showed findings indicative of CSVT: 5 had superior sagittal sinus thrombosis, 5 had transverse sinus thrombosis, 2 had sigmoid sinus thrombosis, 1 had inferior sagittal sinus thrombosis, and 1 had extensive CSVT. **Conclusion:** While we had a CSVT rate of 9.2% which is compatible with previous studies before the pandemic period; in this retrospective study covering the pandemic period, we detected CSVT in 38.8% of patients with suspected PTC. We think that CSVT should be investigated in all patients who are considered to have increased intracranial pressure with combined MRI-MRV imaging.

Keywords: Pseudotumor cerebri; cerebral sinus venous thrombosis; coronavirus disease-2019; papilledema; magnetic resonance venography

ÖZET Amaç: Psödotümör serebri (PTS) nedenleri arasında serebral sinüs ven trombozunun (SSVT) artan sıklığına ve COVID-19 pandemisi sırasında papilödem ile başvuran hastalarda bunun araştırılmasının gerekliliğine dikkat çekmek. **Gereç ve Yöntemler:** COVID-19 pandemisinin başlangıcından itibaren üçüncü basamak bir nörooftalmoloji kliniğinde PTS tanısı konan 44 hastanın tam oftalmolojik muayeneleri, manyetik rezonans görüntüleme (MRG) ve kontrastlı manyetik rezonans venografi (MRV) verileri kaydedildi. Lomber ponksiyon ile intrakraniyal basınç artışı belgelenmeyen, beyin omurilik sıvısı biyokimyası ve mikrobiyolojisi analizlerinde anormallikleri olan ve MRG'de intrakraniyal kitle, obstrüktif hidrosefali veya menenjit tespit edilen hastalar çalışma dışı bırakıldı. **Bulgular:** COVID-19 pozitifliği olan 44 hastanın 36'sında MRG ve kontrastlı MRV görüntülemeleri birlikte değerlendirildi. Çalışmaya dâhil edilen hastaların yaş ortalaması 36,9 idi (minimum: 9-maksimum: 63). Bu 36 hastanın 14'ünde (%38,8) SSVT lehine bulgular saptandı: 5 hastada süperior sagittal sinüs trombozu, 5 hastada transvers sinüs trombozu, 2 hastada sigmoid sinüs trombozu, 1 hastada inferior sagittal sinüs trombozu, 1 hastada yaygın serebral sinüs ven trombozu tespit edildi. **Sonuç:** Pandemi öncesi dönemde yapılan önceki çalışmalarla uyumlu olarak SSVT oranımız %9,2 iken, pandemi dönemini kapsayan bu retrospektif çalışmada PTS şüphesi olan hastalarda %38,8 oranında SSVT tespit ettik. Artmış intrakraniyal basınç olduğu düşünülen tüm hastalarda kombine MRG-MRV görüntüleme ile SSVT'nin araştırılması gerektiğini düşünüyoruz.

Anahtar Kelimeler: Psödotümör serebri; serebral sinüs venöz trombozu; koronavirüs hastalığı-2019; papilödem; manyetik rezonans venografi

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Pseudotumor cerebri (PTC), also known as idiopathic intracranial hypertension (IIH), is defined as high intracranial pressure and the absence of hydrocephalus or intracranial mass lesion to explain this high pressure.[1,2] The underlying etiopathogenesis is not fully understood. The population in which PTC is most common in young or middle-aged women.[3] It is characterized by headache and papilledema. Although papilledema is a characteristic finding in PTC patients, rarely it may present with temporary vision loss, double vision and 6th cranial nerve palsy.[4-7]

Cerebral sinus venous thrombosis (CSVT) is a life-threatening clinical condition that must be considered among the differential diagnosis of all patients with PTC.[8,9] It has been seen in previous studies that the incidence of CSVT in patients diagnosed with PTC was 9.4%.[10] Combined use of magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) has been recommended in the diagnosis of these patients.

While the whole world is struggling with the severe acute respiratory syndrome-coronavirus-2 coronavirus disease-2019 (COVID-19) pandemic, it has been determined that this virus increases the risk of thromboembolic events and coagulopathy.[11] Here, we report the incidence of CSVT in PTC cases diagnosed during the COVID-19 pandemic.

MATERIAL AND METHODS

This retrospective study was arranged according to the Declaration of Helsinki and ethics approval was granted by the Ethics Committee of University of Health Sciences Ankara Bilkent City Hospital (date: January 11, 2023, no: E1/3196/2023). The study was carried out by the Ankara Bilkent City Hospital Department of Ophthalmology, Neuro-ophthalmology Unit and informed consent was obtained from all patients included in the study. The files and cranial MRI-MRV reports of patients diagnosed with PTC in the period from January 2020, when the COVID-19 pandemic began, to the present, were retrospectively scanned. Ophthalmological examinations of all patients were performed by the same clinician who specializes in neuro-ophthalmology unit. Visual acuities which were measured using the Snellen chart and visual field measurements are routinely performed with the same parameters for all patients during diagnosis and subsequent disease progression and treatment follow-up.

PTC is determined according to the modified Dandy criteria: 1) Symptoms and signs such as headache, nausea, vomiting, papilledema that may be associated with increased intracranial pressure, 2) Cerebrospinal fluid (CSF) opening pressure greater than 25 cm H_2O with normal CSF composition, 3) Absence of abnormal neurological findings other than 6th cranial nerve palsy, 4) Absence of space-occupying lesions in neuro-radiological imaging. Patients with CSVT detected on cranial MRI and MRV imaging were separated from the idiopathic group and their files were evaluated.[4,5]

Age and gender of all patients included in the study were recorded. Visual acuities which was measured using the Snellen chart, anterior segment examination, fundus examination, whether cranial MRI and contrast-enhanced MRV were performed in all patients, and whether there is a finding in favor of thrombosis in cranial MRI and MRV were noted.

Patients without a documented increase in intracranial pressure by lumbar puncture, patients with abnormalities in CSF biochemistry and microbiology analysis, and patients with intracranial mass, obstructive hydrocephalus, meningitis on MRI were not included in the study.

There was no need for an extra element of safety for the research team and patients other than insurance or hospital rules. The research, in its current form, did not require insurance, as it did not pose any risk to patients.

RESULTS

A total of 44 patients who were diagnosed with PTC from the beginning of 2020, when the COVID-19 pandemic broke out, to the present, were included in the study. There was no age or gender discrimination among the patients included in the study. The mean age of the included patients was 36.9 years (minimum: 9-max: 63). All the patients whose files were retrospectively scanned had a history of confirmed COVID-19 positivity through PCR testing. None of

the patients were experiencing acute COVID-19 infection. All patients had COVID-19 disease without hospitalization. They did not specify the medication they used chronically. All of our patients had blind spot enlargement and peripheral concentric narrowing, which are classic findings in PTC, in varying degrees of visual field testing. Optic disc edema was bilateral in the fundus examinations of all patients. MRI and contrast-enhanced MRV imaging were evaluated together in 36 of these 44 patients, and it was seen that MRV examination was not requested in 8 patients. Of the 36 patients who underwent combined imaging, 28 were female and 12 were male. When imaging results of 36 patients for whom MRV was requested, we found findings in favor of CSVT in 14 patients (38.8%). Of these 14 patients, 8 were female and 6 were male. Upon examination of their files, the detection of CSVT occurred approximately 4-6 months after their initial COVID-19 infection. Of these patients, who were found to have thrombosis based on the data obtained from MRV imaging, 5 had superior sagittal sinus thrombosis, 5 had transverse sinus thrombosis, 2 had sigmoid sinus thrombosis, 1 had inferior sagittal sinus thrombosis, and 1 had extensive cerebral sinus venous thrombosis.

DISCUSSION

The optic disc swelling, which occurs due to the increased intracranial pressure, described as papilledema. PTC is a syndrome of increased intracranial pressure without hydrocephalus or mass lesion and with normal CSF composition.PTC is characterized by headache and optic disc edema in classical. Although optic disc edema is classically seen in PTC, in some cases edema may be asymmetrical in different stages and in rare cases and in secondary intracranial hypertension that has gone through atrophy, edema may not be seen.[1-5]

PTC, which is diagnosed after excluding causes of elevated intracranial pressure, headache, and bilateral optic disc edema, is actually a diagnosis of exclusion. In the diagnosis of PTC, radiological evaluation is classically made with orbital and cranial MRI, and an increase in the transverse diameter of the globe, optic nerve thickness and perioptic CSF range is seen in the axial sections of the orbit. It is possible to show the presence of posterior scleral flattening, vertical tortuosity, papillary protrusion and "empty sella" in sagittal and axial images. However, MRI may be normal in some cases.[3]

CSVT is a rare form of venous thromboembolism that may present with acute focal/generalized neurological symptoms such as headache, seizures, changes in sensory organs, aphasia and diplopia.[6,7] The most commonly affected areas are dural sinuses, superior sagittal sinuses, transverse and sigmoid sinuses. Although CSVT is considered a rare entity. It can cause death and paralysis if its diagnosis is delayed. However, patients with subacute/chronic CSVT may present with clinical manifestations of IH such as blurred vision, transient vision loss, diplopia and papilledema. These patients may be misdiagnosed as IIH or disc edema due to other etiologies. In addition, MRI may be normal in up to 30% of these patients.[8] Occasionally, there may be asymmetric or unilateral disc edema, suggesting other causes of optic neuropathy. There is an obese, blond, middle-aged, female patient profile that is typical for idiopathic PTC. Male gender, absence of obesity, use of oral contraceptives, deep vein thrombosis, hypercoagulant states, lupus anticoagulant, ear, nose and throat infections, mastoiditis, and history of surgery in the head and neck region require consideration of etiological factors that deviate from typical PTC. Therefore, we emphasize that when intracranial hypertension is detected, it should be considered in patients other than middle-aged, obese women, where this disease is typically seen. However, we think that it should be investigated in all patients, especially in the patient group specified as typical for PTC, especially after COVID-19 infection during the pandemic period.[9-11]

Cases of IH with CSVT have been reported during the pandemic period.[12-14] As stated in studies covering the pandemic period, the condition may mimic idiopathic IH by appearing acutely during COVID-19, in the form of CSVT, papillophlebitis or meningoencephalitis, therefore a high index of suspicion is required in these cases.[15] In our patient group, patients known to have had COVID-19 have IH due to CSVT, which develops as a result of possible coagulation disorder, as a sequela. Since we examined the

patients referred to us because they developed IH in our study, we considered it as a sequela.

Determining the etiology of IH is important in terms of symptoms and treatment. Because in CSVT, it is necessary to treat coagulation as well as increased pressure. Research and treatment plans should be made in terms of causes of coagulation disorder.[16,17] While we had a CSVT rate of 9.2% which is compatible with previous studies before the pandemic period, this rate increased to 38.8% during the pandemic period, and the history of exposure to coronavirus in patients with CSVT at varying times also supports the effects of COVID-19 on coagulation.[18,19] It has been reported that coagulopathy may be responsible in cases where elevated CSF pressure was detected without meningitis or encephalitis in the lumbar puncture (LP) results performed for CSF analysis during the pandemic period.[20]

During the COVID-19 pandemic, tracking cases of IH, like all chronic diseases, proved challenging. Nevertheless, diagnosis could be established by observing papilledema in patients presenting with headaches and visual field defects. In the study of Agarwal et al. it was reported that CSVT was detected in 11.4% of patients who were predicted to have IIH.[21] CSVT may be missed in patients who do not have concomitant MRV while MRI is being performed. We think that in patients who cannot be diagnosed correctly, they may continue to be treated as IIH, and may lead to optic atrophy, paralysis and death. Therefore, MRV in combination with MRI is definitely recommended to identify this subgroup of patients, except for obese patients with classic PTC profile and risk factors for CSVT.[10]

The major limitations of the study were that it was a retrospective design and the number of patients was not large enough.

MRI or MRV alone can cause false positive and false negative results. The main shortcomings of MRI in the diagnosis of CSVT are flow artifacts and temporal variation of signal return by thrombus. Second, MRI scans performed early and late in the course of the disease make false negative results more likely. Adding MRV to cranial MRI will increase the accuracy of the diagnosis. The combination of MRI and MRV is the preferred diagnostic method for CSVT. Various neuroimaging methods have been used in the studies to detect CSVT. Consistent with previous studies, the use of MRV combined with MRI can be considered the most accurate and easiest method.[22-24]

After COVID-19 was detected in our country during the pandemic period, all clinically necessary cases were hospitalized and all tests were performed, and thrombolytic treatment was given to patients with a general thromboembolism risk, along with other treatments. However, patients with a mild course were not hospitalized due to the high number of cases in this period. What we want to emphasize is that the possibility of CSVT increases even in mild cases during the pandemic period. Therefore, we think that the possibility of CSVT should be excluded in all patients diagnosed with PTC.

CONCLUSION

Cranial MRI is routinely requested by neurology and neuro-ophthalmology clinics in all patients suspected of having increased intracranial pressure. However, this study emphasizes that CSVT should not be overlooked with the MRV test and that MRV should be added to the routine. In conclusion, while we had a CSVT rate of 9.2% which is compatible with previous studies before the pandemic period in this retrospective study covering the pandemic period, we detected CSVT in 38.8% of patients with suspected PTC. Therefore, we think that CSVT should be investigated in all patients who are considered to have increased intracranial pressure with combined MRI and MRV imaging.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Mualla Hamurcu, Bilge Tarım;* ***Design:*** *Mualla Hamurcu, Bilge Tarım;* ***Control/Supervision:*** *Mualla Hamurcu;* ***Data Collection and/or Processing:*** *Bilge Tarım;* ***Analysis and/or Interpretation:*** *Mualla Hamurcu;* ***Literature Review:*** *Bilge Tarım, Mualla Hamurcu;* ***Writing the Article:*** *Bilge Tarım;* ***Critical Review:*** *Mualla Hamurcu;* ***References and Fundings:*** *Mualla Hamurcu, Bilge Tarım;* ***Materials:*** *Mualla Hamurcu.*

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