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Watershed Venous Infarcts Accompanying Cerebral Venous Sinus Thrombosis: A Case Report of Two Cases and a Literature Review

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Abstract

Cerebral Venous Sinus Thrombosis (CVST) is a rare disease affecting young and female patients in particular. Watershed infarct areas are rarely observed in CVST and in cases where they are observed, they usually occur as a result of the involvement of deep venous structures. The definitive diagnosis of CVST is established by magnetic resonance venography. In addition, this article also includes a review of the cases with established CVST and watershed infarct areas reported in the literature. It should be kept in mind that in patients with watershed infarct areas and severe headache, the etiology may include cerebral venous thrombosis.

Keywords: Cerebral venous sinus thrombosis; Watershed infarction; Prognosis; Magnetic resonance venography

Introduction

Cerebral Venous Sinus Thrombosis (CVST) rarely occurs as compared to arterial stroke, accounting for 0.5% of all strokes [1]. Its diagnosis can sometimes be delayed due to a wide spectrum of symptoms associated with it ranging from headache to coma. Nevertheless, the use of imaging methods such as Magnetic Resonance Venography (MRV) in the recent period facilitated the establishment of a final CVST diagnosis. CVST often affects the female gender, and hence gynecological causes such as pregnancy, postpartum period and oral contraceptive use are at the forefront in its etiology. There are also cases in whom CVST was reported recently after having a SARS-CoV-2 vaccine [2]. A significant increase in the incidence of CVST was observed following the emergence of COVID-19 breakout.

In CVST, venous infarct, hemorrhagic venous infarct and even though rarely watershed infarct areas can be observed in radiological imaging. There are only a few case reports of venous watershed infarction available in the literature [3-6]. In view of the foregoing, it is aimed with in this study to investigate the clinical course, prognosis and treatment of two patients with CVST accompanied by venous watershed infarction, who were being followed up in the institution, where this study was conducted.

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Case 1

A 40-year-old male patient with complaints of severe headache, nausea, vomiting, and altered consciousness, to the emergency department in June 2021. It was learned that the patient had been vaccinated with a viral vector vaccine against SARS-CoV-2 2 days ago, and that the headache, which started one day after the vaccination, became increasingly severe. His neurological examination revealed that he was conscious, had distorted time orientation, and was partially cooperative. His laboratory tests revealed White Blood Cell (WBC) count as $20.38 \times 10^3/\mu L$ (normal range: $3.9 \times 10^3/\mu L$ to $10.8 \times 10^3/\mu L$), neutrophil count as $11.64 \times 10^3/\mu L$ (normal range: $1.91 \times 10^3/\mu L$ to $7.61 \times 10^3/\mu L$), lymphocyte count as 9% of the total WBCs (normal range: 18% to 47%); C-Reactive Protein (CRP) as 32.22 mg/L (normal range: 1 mg/L to 5 mg/L), platelet count as $209 \times 10^3/\mu L$ (normal range: $145 \times 10^3/\mu L$ to $345 \times 10^3/\mu L$), fibrinogen as 530 mg/dL (normal range: 245 mg/dL to 400 mg/dL), vitamin B12 as 64 pg/mL (normal range: 126 pg/mL to 505 pg/mL), and homocysteine as 26.9 µmol/L (normal range: 5 µmol/L to 15 µmol/L). Cerebral venous thrombosis and watershed infarct areas were observed in Magnetic Resonance Imaging (MRI) of the patient (Figure 1). Computerized cerebral angiography of the patient who had watershed infarct areas did not reveal arterial ischemia.

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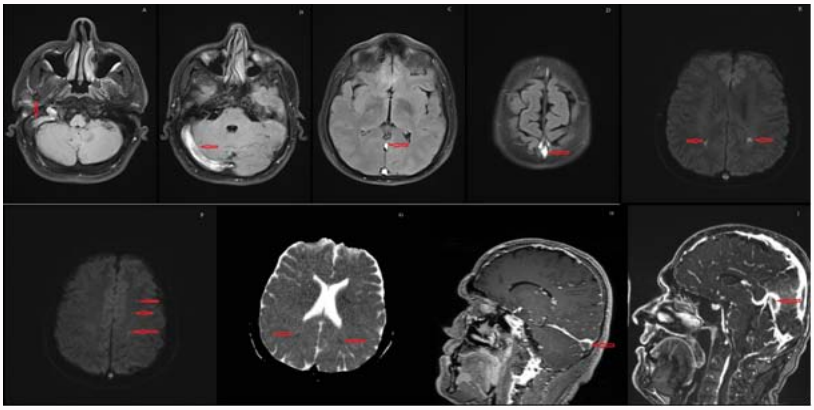

Figure 1: In the first case, brain MRI revealed in FLAIR sequence an appearance compatible with hyperintense thrombus in the right sigmoid sinus (A), right transverse sinus (B), straight sinus (C), and superior sagittal sinus (D). Bilateral watershed infarct areas with marked diffusion restriction were observed on DWI on the left (E-G). Thrombus material compatible with CVST was observed in contrast-enhanced MRV (H,I).

Table 1: Clinical and radiological features of patients with venous watershed infarction.

	Patient 1	Patient 2	Tan	Washidaat al.	Ravinder-JeetSiinghat al.	Şimşek at al.
Age (year)	40	55	15	67	30	39
Sex	Male	Female	unspecified	Male	Female	Male
Etiologicalcause	SARS-CoV-2 vaccination	Hyperfibrinogenemia	Neurosurgical intervention	Dehidratasyon	unspecified	Infection (COVID-19) and genetics
Symptoms and signs	Headache, nausea-vomiting, altered consciousness	Headache, altered consciousness	Seizures, left-sided spastichemiplegia, and visual field deficits	Headache, vomiting, altered consciousness	Headache, vomiting, left hemiparesis, altered consciousness	Headache
Fibrinogen (245-400 mg/dL)	530	472	unspecified	N	unspecified	N
Protein C	N	N	unspecified	N	unspecified	N
Protein S	N	N	unspecified	N	unspecified	N
ATIII	N	N	unspecified	N	unspecified	N
Genetic testing	Homozygous MTHFR and heterozygous FV *H1299R* gene mutations	Heterozygous FV *H1299R* gene mutations	unspecified	N	unspecified	Heterozygous *MTHFR* and *FVL* gene mutations
MRI findings	Watersheed infarct areas on diffusion-weighted images	Watersheed infarct areas on diffusion-weighted images, Swelling of the left thalamus in FLAIR sequence	Diffusion-weighted imaging showed foci of restricted diffusion in the right cerebral deep white matter	Watersheed infarct areas on diffusion-weighted images, symmetrical swelling of the bilateral thalamus and basal gagnions in FLAIR sequence	Thalamic and basal ganglia signal changes and bilateral centrum semiovalpunctate infarcts	Venous infarct area in the right thalamus and diffusion-weighted images revealed watershed infarct areas
MRV/CTV findings	Right transverse sinus, straight sinus, superiorsagittal sinus thrombosis	Thrombus in all superficial and deep cerebral veins	Right internal cerebral vein thrombosis.	Straight sinus and galen vein thrombosis	Straight sinus thrombosis	Bilateral transverse-straight-superiorsagittal sinus, right internal cerebral vein, and thrombus in the right thalamostriatvein
Treatment	Warfarin sodium	Warfarinsodium	unspecified	Heparin	Unfractionated Heparin	Warfarin sodium
Conclusion	Discharged	Discharged	Discharged	Discharged	Discharged	Discharged

ATIII: Anti-Thrombin 3; FLAIR: Fluid Attenuated Inversion Recovery Imaging; CTV: Computed Tomography Venogram; LMWH: Low Molecular Weight Heparin; MTHFR: Methylenetetrahydrofolate reductase; FVL: Factor V Leiden Gene Mutations; N: Normal; MRI: Magnetic Resonance Imaging; MRV: Magnetic Resonance Venography

His vasculitis markers were normal. His genetic analysis revealed homozygous methylene tetra hydrofolate reductase and heterozygous factor V *H1299R* gene mutation (Table 1). The patient was discharged with warfarin sodium. Partial recanalization was observed in the follow-up MRV taken two months later.

Case 2

A 55-year-old obese female patient with known pre-existing hypertension was admitted to the emergency department in May 2021. The patient, who was learned to have a headache for the last few days, had been brought to the emergency room due to a change in her consciousness in the morning. During her neurological examination, her eyes were spontaneously open, she did not answer the questions addressed to her, and she made meaningless sounds and appeared apathetic. Her all four extremities were mobile, and her right upper extremity was lagging behind as compared to her left upper extremity. There was no neck stiffness, and the response of the plantar reflex was a bilateral extensor response. Cerebral venous

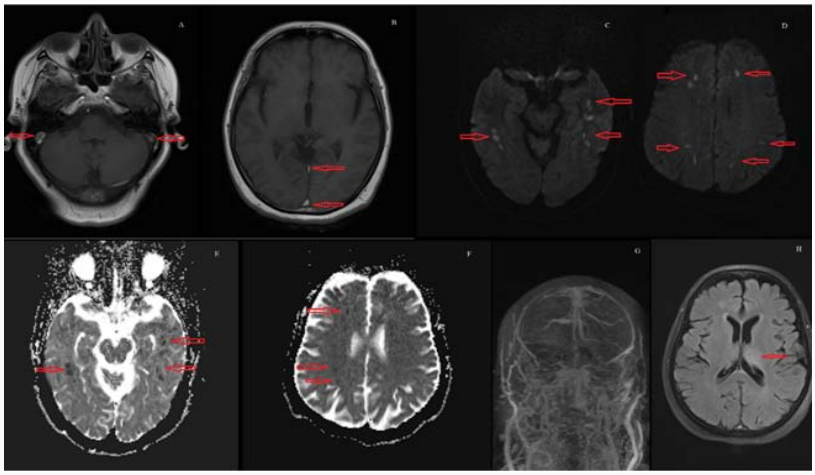

Figure 2: In the second case, brain MRI revealed in T1 sequence an appearance compatible with hyperintense thrombus in bilateral transverse sinus (A), straight sinus and superior sagittal sinus (B). Watershed infarct areas with bilateral diffusion restriction were observed on DWI (C-F). Contrast-enhanced MRV revealed filling defect in all superficial and deep veins (G) and hyperintense swelling in the left thalamus in FLAIR sequence (H).

thrombosis and watershed infarct areas were observed in Magnetic Resonance Imaging (MRI) of the patient (Figure 2). The results of her computed cerebral angiography were normal. Her laboratory tests revealed WBC count as 13.47 × 10^3/μL (normal range: 3.9 × 10^3/μL to 10.8 × 10^3/μL), platelet count as 209 × 10^3/μL (normal range: 145 × 10^3/μL to 345 × 10^3/μL), C-Reactive Protein (CRP) as 17.1 mg/L (normal range: 1 mg/L to 5 mg/L), and fibrinogen as 472 mg/dL (normal range: 245 mg/dL to 400 mg/dL). She did not have any focal and systemic infection foci. Her vasculitis markers were normal. Her genetic analysis revealed heterozygous factor V *H1299R* gene mutation. Her malignancy scan was clear. The etiologic cause was thought to be hyperfibrinogenemia, taking into consideration the persistent high fibrinogen levels found in repeated examinations. The patient was discharged with warfarin sodium. Her MRV taken one week later revealed partial recanalization, and her clinic had significantly improved.

Discussion

There is no effective drug therapy in the fight against COVID-19, and the most effective way to be protected from COVID-19 is to try to prevent the spread of the COVID-19 through vaccination. There are two types of vaccines, viral vector vaccines and messenger RNA (mRNA) vaccines. CVST is one of the serious side effects seen in association with the administration of mRNA vaccines, albeit rare. Vaccine-induced thrombocytopenic thrombosis is blamed for this serious side effect [7,8]. However, in addition to cases with CVST accompanied by thrombocytopenia, cases who developed thromboembolic events without thrombocytopenia have also been reported during the post-vaccination period. In parallel, in the study of Perry et al. [9], in which cases that developed CVST after vaccination against COVID-19 were examined, vaccine-induced immune thrombocytopenia was observed in 70 of the 95 CVST patients, while the remaining 20 patients did not develop thrombocytopenia [9]. In comparison, the first case presented in this study developed CVST on the second day after vaccination. This is different than the results reported in the literature in that the cases presented in the literature were reported to have developed thrombosis within 4 to 19 days after vaccination. The platelet count of the patient was normal, however he was found to have hyperhomocysteinemia, vitamin B12 deficiency and homozygous MTHFR (Methylenetetrahydrofolate Reductase) mutation. Accordingly, the presence of additional risk factors is thought to have predisposed the patient to thrombosis, which caused the patient to develop thrombosis as early as on the second day after vaccination. This result raises the question whether genetic examination, homocysteine, vitamin B12 level and other coagulation factors should be checked before vaccination, even if the patients do not have a history of thromboembolic events. On the other hand, the etiology of the second case presented in this study included hyperfibrinogenemia as well as obesity as a predisposing factor. Brain MRI revealed venous watershed infarct areas in both of the cases investigated in this study, and a dramatic improvement was observed in their clinics after treatment. There was extensive thrombus in both deep and superficial veins in the second case presented in this study, yet the fact that recanalization was observed in the follow-up MRV taken on the 7th day suggests that early diagnosis and treatment were effective on the prognosis.

In CVST, venous pressure increases secondary to obstruction, whereas capillary perfusion decreases. Initially the cerebral collateral network tolerates this pressure, yet venous stasis, vasogenic edema, and hemorrhagic infarctions occur in the later period as the capacity of the collateral network is exceeded. Decreased cerebral perfusion causes cytotoxic edema and increased intracranial pressure. There are studies in which it was demonstrated on diffusion-weighted imaging (DWI) that the resulting increase in intracranial pressure causes ischemia [10]. The reported etiological causes of patients with watershed infarcts secondary to CVST in the literature vary. The course of the disease was not mortal in any of these patients, and clinical improvement was observed in all of them after treatment. Deep venous thrombosis was common to all these patients. Presence of deep venous thrombosis indicates a poor prognosis as venous watershed infarcts are seen in relation thereto, but there were no patients with a mortal course among the reported cases.

In conclusion, early diagnosis seems to be a very effective parameter in prognosis. Additionally, the presence of genetic mutations in the two cases presented in this study in association with COVID-19 infection and COVID-19 vaccination suggests that genetic tests should be carried out in these patients.

Watershed infarct areas are mostly observed in hypotensive cerebral infarction. Differential diagnosis is important since different

treatments are indicated in arterial and venous watershed infarcts. It should be kept in mind that CVST may be present in patients with watershed infarct areas and clinically prominent headache, and that watershed infarcts may be of venous origin, albeit rarely.

Highlights

- Watershed infarcts are not always arterial.
- Cerebral venous thrombosis should be excluded in the presence of headache and watershed infarct.
- Heparin may worsen the clinic in thrombosis induced by COVID-19 infection.

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