Rare case of Simultaneous Cerebral Artery and Venous Sinus in Thrombosis in setting of elevated factor VIII and use of combined oral contraceptive pills.

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September 22, 2021

Abstract

We report a rare and first case of combined cerebral venous sinus thrombosis and posterior internal carotid artery stroke in a 35-year-old female on combined oral contraceptive pills (COCP), presented with headache and vertigo, found to have extensive venous thrombosis and PICA territory ischemic infarct with persistently elevated factor VIII.

CASE REPORT

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Key Words: Stroke, Thrombosis, Cerebral Artery, Cerebral Venous Sinus, Factor VIII.

ABSTRACT

We report a rare and first case of combined cerebral venous sinus thrombosis and posterior internal carotid artery stroke in a 35-year-old female on combined oral contraceptive pills (COCP), presented with headache and vertigo, found to have extensive venous thrombosis and PICA territory ischemic infarct with persistently elevated factor VIII.

Key Clinical Message:

Owing to limited reports of simultaneous CVST and ischemic stroke. physicians must have low threshold to include Factor VIII as a in thrombophilia work up, as a possible factor to arterial and venous thrombosis.

INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is a cerebrovascular disease characterized by thrombosis intracranial veins and sinuses. It is an unusual and unrecognized form of stroke that accounts for approximately 0.5 to 1% of strokes.[1] CSVT can occur among all age groups, but peak incidence is observed in new-borns, neonates, and middle-aged individuals in their third decade of life, with female to male ratio of 3:1. [2]

The etiology of CSVT is multifactorial. Once the diagnosis is confirmed, it warrants a further detailed approach to identify the cause. In comparison to arterial ischemic strokes, CSVT may progress over days. Based on the involved venous sinus location, there is a broad spectrum of clinical presentation, such as seizures, headache, altered level of consciousness, and focal neurological signs/symptoms. According to the most extensive cohort study on CSVT, the International Study on Cerebral Venous and Dural Sinuses Thrombosis (ISCVT), 37% of patients present with acute onset (<48 hours), 56% as subacute (>48 hours to 30 days), and chronic (>30 days) in 7% of patients . [2]

Simultaneous cerebral arterial and venous infarction has been reported in very few case reports. We describe a young lady who presented with headache, dizziness, memory disturbance while on OCP, found to have persistently elevated serum Factor VIII. Neuroimaging confirms the diagnosis of CSVT and PICA thrombosis.

CASE PRESENTATION

A 35year-old Filipino lady, who was previously healthy, presented to our hospital with five days history of severe occipital headache and dizziness. She described dizziness as vertigo. It was progressively worsening over the last two days. She complained of nausea, vomiting, and memory disturbance with difficulties in reading and naming objects. She reported no sensory or motor deficits. There was no trauma or fall. She started taking OCPs for three months. The patient has no personal or family history of coagulopathy. Physical examination revealed horizontal nystagmus in the right gaze with a fast component to the right side. She has mild dysmetria and ataxia. There is a problem with word-finding and dyslexia. The rest of the physical examination was unremarkable.

Laboratory investigations showed normal complete cell counts. Vasculitis screen, including antiphospholipid syndrome, was negative, and complement level was normal. Thrombophilia screen revealed normal protein C and S levels. Factor V Leiden mutation was absent, but she has high levels of factor VIII (243 % reference 70-150 %) repeated factor VIII level within ten days from the first level was 231.7 %

Computed Tomography Image of the head with venogram suggestive of CSVT with hemorrhagic infarct and vasogenic edema in the left temporal-occipital and left vertebral occlusion with left PICA territory infarct (Figure 1).

Magnetic resonance image (MRI) and Magnetic resonance image with Venogram (MRV) were done 24 hours later. Both showed an acute PICA territory infarct involving the cerebellar vermis and left posterior-inferior cerebellar hemisphere with clots in the distal PICA branches. There was a stable left distal vertebral artery occlusion and stable left temporo-occipital venous hypertension, hemorrhage, and infarct. Echocardiogram was normal. (Figure 2)

The patient was initially admitted to the medical intensive care unit (MICU) for close observation. She was evaluated by a neurologist, who advised stopping OCPs and starting therapeutic anticoagulation with low molecular weight heparin (LMWH) enoxaparin (1 mg/kg subcutaneous twice per day) was initiated.

After two weeks of therapeutic anticoagulation, a follow-up CT scan showed almost total resolution of the occipital hyperdensity focus and slightly reduced temporal hyperdensity; and somewhat stable surrounding hypodensity and secondary mass effect on the adjacent sulci. There is a complete resolution of sinus thrombosis. Following this result, therapeutic anticoagulation was stopped, and the patient was started on Aspirin 100 mg and Atorvastatin 20 mg. She was transferred to a rehabilitation center. She received intensive physical and occupational therapy. Four weeks later, the patient was discharged with almost resolution of most of her deficits. She was able to walk with minimal assistant due to mild dizziness.

DISCUSSION:

The incidence of CSVT is estimated to be 0.22 to 1.57 per 100,000, with a more observed propensity in females compared to males of a ratio of 3:1, with 70-80% of cases are female in their childbearing age. This disproportion could be explained by one of the proposed mechanisms of CSVT, attributed to the hypercoagulable state, which is common in pregnancy, puerperium, and combined oral contraceptive use.[2]

Many proposed pathophysiological mechanisms could explain CSVT, with at least two projected. First, thrombosis of cerebral veins or dural sinus impeding blood drainage leading to parenchymal insult and disruption of the blood-brain barrier, secondary to build up of venous and capillary pressure that impairs cerebral blood flow.[3] Secondly, non-resolved venous thrombus impairing cerebrospinal fluid (CSF) absorption via arachnoid granulation and increase intracranial pressure, leading to cytotoxic and vasogenic edema and eventually may cause parenchymal hemorrhage. [3] These mechanisms are demonstrated on neuroimaging such as MRI methods, diffusion-weighted MRI, and perfusion-weighted MRI showing cytotoxic and vasogenic edema .[3]

The etiology and predisposing risk factors of CSVT are several, with Virchow triad, associated with blood stasis, hypercoagulability, and alteration in the vessel wall, being the center of its pathophysiology\sout, For instance, inherited or acquired thrombophilia, Para-meningeal infection, trauma, and neurosurgical procedures, medications, and many inflammatory diseases could attribute as causative factors of CSVT that may exist alone or in a bundle with a synergistic effect. For example, combined oral contraceptive (COC) with co-existing mild to severe inherited thrombophilia such as factor prothrombin gene mutation increases the odds of CSVT. Mutated Factor V Leiden (R506Q) and MTHFR C677T are the most common genetically predisposed thrombophilia, accounting for 10% and 9.3%, respectively, of venous thromboembolism. [4] Factor VIII is a main propagating factor in the coagulation cascade has been attributed to the thrombotic state. One study that looked at elevated serum factor VIII and risk of recurrence of venous showed, serum levels greater than 150 mcg/L are associated with a 5-fold risk for venous thrombosis. [4]

In a systematic review and meta-analysis on COC, thrombophilia and the risk of venous thromboembolism, demonstrated; risk of VTE in COC users with mild to severe thrombophilia is 6-fold higher with a rate ratio [RR], 5.89; 95% confidence interval [CI], 4.21–8.23) and 7-fold (RR, 7.15; 95% CI, 2.93–17.45), respectively. Cochrane reviews noted that the use of combined oral contraceptives increased the risk of venous thrombosis (relative risk (RR) 3.5, 95% confidence interval (CI) 2.9 to 4.3). as well as arterial thrombosis (RR1.7, 95% CI 1.5 to 1.9) compared with non-use [5]

Interestingly enough, Factor VIII is a propagating factor in both intrinsic and extrinsic coagulation pathways, which is stabilized by the von Willebrand factor complex (vWF). [6] Although its level can be high in as acute phase response in the setting of acute strokes, in a study by O'Donnell et al., half of their patients showed elevated Factor VIII that could be attributed to vWF, which supports the notion that elevated factor VIII remains the driving force behind thrombotic events. [6]

Factor VIII relevance in prothrombic syndrome was first recognized in 1990, where hemophiliac patients with factor VIII deficiency had a protective effect against coronary heart diseases. [7]Over the past few years, compelling evidence showed the risk of arterial thrombosis in patients for elevated serum Factor VIII. Folsom et al. conducted a prospective study on over 15,000 patients without cardiovascular risk factors, reported 191 ischemic strokes events that had Factor VIII in the uppermost quartile showed an adjusted relative risk factor of 1.93. [8]

Our patient presented with a rare combination of veno-arterial disease (ischemic stroke with CSVT), which had elevated factor VIII of 231.7 and 243.5% provoked by OCP use. Previously, CSVT has been linked with the use of oral contraceptives, with its risk being higher in genetically predisposed patients with underlying thrombophilia. Furthermore, OCP is considered a risk factor for ischemic stroke. According to the WHO, the odds ratio for ischemic stroke in women who take oral contraceptives is 2.99 (1.65 to 5.40). [1]

However, our case differs from those reported in the literature in that the patient suffered from concomitant

CSVT and ischemic stroke (specifically PICA distribution). Her presentation resulted from 1.6-fold higher serum Factor VIII provoking a thrombotic state in the setting of oral contraceptive use. In addition, our patient presented with headache and nausea and was found to have cerebellar signs, and she had quick recovery clinically and radiologically.

Conclusion:

A concomitant arterial and venous thrombosis (Ischemic stroke and CVST) in a young female with no vascular risk factors is a rare event and was not reported in the literature before. The patient's prothrombotic state can be explained by the high factor VIII levels and the fact that the patient was on OCP. Further studies and recommendations regarding the use of OCPs in patients with high prothrombotic factors.

ACKNOWLEDGMENT

The authors would like to acknowledge Qatar national library (QNL) for this publication's funding and the HMC internal medicine residency program for scientific support.

CONSENT

Written informed consent was obtained from the patient for the publication of this case report.

ETHICAL APPROVAL

This case report was approved by the Hamad Medical Corporation's Medical Research Center (Protocol number: MRC-04-21-575)

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on request.

AUTHOR CONTRIBUTIONS

Writing the initial draft of the manuscript: *AS, OH,AM, AA, SS.*

Conceptualization and supervision: *SS, AAZ*

Medical management of the case: *AS, OH, AM, AA, SS, AAZ*

Revising the manuscript critically and literature review: *AS, OH,AM, AA, SS, AAZ*

Appendix 1

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