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ANEMIA: AN UNCOMMON CAUSE OF CEREBRAL VENOUS SINUS THROMBOSIS

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ABSTRACT

Cerebral venous sinus thrombosis (CVST) is a multifactorial illness seen more commonly in females as compared to males. Its diagnosis is often delayed due to variable clinical presentations. It is now identified more often due to advancements in neuroimaging modalities. We present an uncommon case of CVST caused by anemia in a 23-year-old female. Our patient presented with complaints of headache since the past two days and left sided hemiplegia since past one day. Later on during her hospital stay she developed generalized tonic clonic seizures. MRI and MRV brain with contrast revealed right cerebral venous (vein of Trolard) thrombosis. Blood tests showed hypochromic microcytic anemia which was the likely precipitating factor in our case as thrombophilia factors were normal. Headache and focal neurological symptoms should raise suspicion of CVST in anemic patients. Early commencement of anticoagulation along with correction of underlying cause, anemia in this case, leads to better prognosis.

Keywords: Seizures; CVST; Anemia

INTRODUCTION

A rare cerebrovascular illness, cerebral venous sinus thrombosis (CVST) mostly affects children and young adults.[1] With a 3:1 female to male ratio, there is more likelihood of developing in females relatively as compared to males. Despite being less prevalent than arterial stroke, it is now identified more often as a result of advancements in neuroimaging modalities. Its diagnosis can often be difficult due to subtle and variable clinical presentations. Incidence of CVST ranges from 0.22 to 1.57 per 100,000 people annually. Patients with CVST often appear at a median age of 37 years old.[1] Up to 80% of patients have identifiable risk factors. The primary risk factors for CVST can be either noninfectious or infectious. The most common non-infectious causes are cancer, granulomatous or inflammatory disorders, and connective tissue disorders. Nevertheless, 20% to 35% of cases have no obvious cause.[1,2] We present an uncommon case of CVST caused by anemia in a 23 years old female.

CASE PRESENTATION

A 23-year-old unmarried female, presented to PAF Hospital Islamabad with sudden onset of throbbing, persistent headache, which was initially diffuse but later localized to temporal region. Later she developed left hemiparesis which was progressive in nature. She had no history of falls or any similar episode in the past. There was no associated paresthesias, fever, blurring of vision, speech abnormality or bowel and bladder involvement. During hospital stay she developed left sided jerky movements followed by generalized tonic clonic seizures which were managed immediately with anti-seizure drugs.

She was diagnosed with anemia two months back for which she did not seek any medical treatment. The cause of anemia was likely nutritional as there was no history of blood loss.

Gynecological history included menarche at the age of 16 and regular menstrual cycles. Drug history was unremarkable. No significant family history of stroke or thrombosis was reported.

She was markedly pale on examination. Her Glasgow coma scale was 15/15. Neurological examination revealed upper motor neuron type weakness on left side as evident by hypertonia, left hemiparesis, brisk reflexes with ill sustained left ankle clonus and positive left Babinski sign. Bilateral sensations were intact. Pupils were equal and reactive. Fundoscopy was normal. There were no signs of meningeal irritation or raised intracranial pressure.

The results of all the blood tests, including the thrombophilia screening investigations are mentioned in Table 1.

Table 1: Laboratory and Thrombophilia Screening Results		
Investigation	**Patient's Result**	**Normal Range**
Hemoglobin	5.1 g/dL	12–15 g/dL
MCV (Mean Corpuscular Volume)	64 fL	80–100 fL
TLC (Total Leukocyte Count)	6.5 × $10^3/\mu L$	4–11 × $10^3/\mu L$
Platelet Count	436 × $10^9/L$	150–400 × $10^9/L$
Ferritin	3 ng/mL	12–150 ng/mL
Folate Level	0.802 ng/mL	3–17 ng/mL
Vitamin B12	166 pg/mL	200–900 pg/mL
Peripheral Smear	Anemia, anisocytosis, microcytosis, increased	
platelets	—	
Bone Marrow Examination	No abnormal cells	—
Hemoglobin Electrophoresis	No hemoglobin disorder detected	—
ANA	Negative	—
VDRL	Negative	—
Lupus Anticoagulant	45 s	35–53 s
Antithrombin III	89 %	75–125 %
Factor V Leiden	1	>0.8
Protein C Normalised Ratio	0.74	>0.8
Protein C Activation Time (PCAT)		
60 s	85–200 s	
PCAT/O (without activator)	37 s	35–55 s
Anti-Cardiolipin Antibodies IgG	1 U/mL	<10 U/mL
Anti-Cardiolipin Antibodies IgM	2 U/mL	<10 U/mL

CT scan brain plain was unremarkable and cerebrospinal fluid routine examination was normal. MRI (figure 1) and MRV brain with contrast (figure 2) revealed right cerebral venous (vein of Trolard) thrombosis with extension into the draining segment of superior sagittal sinus. It was causing venous infarction with minor hemorrhagic component within the right parietal lobe.

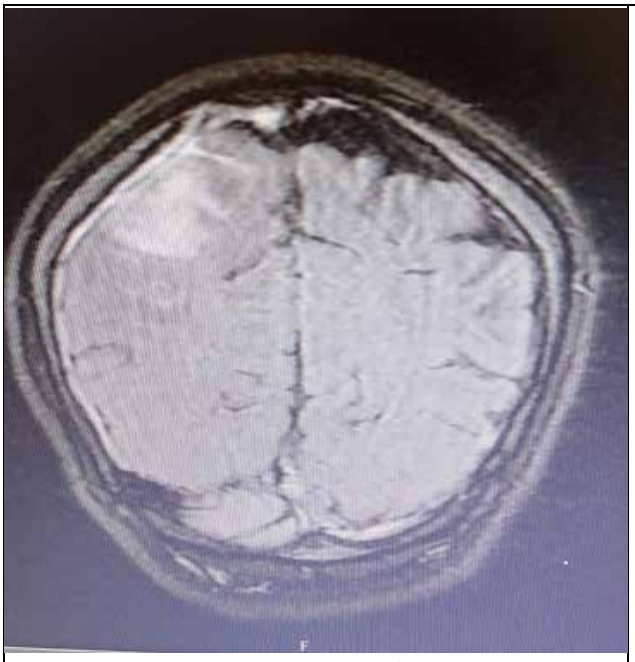

Figure 1 - MRI Brain showing venous infarction with minor hemorrhagic component within the right parietal lobe.

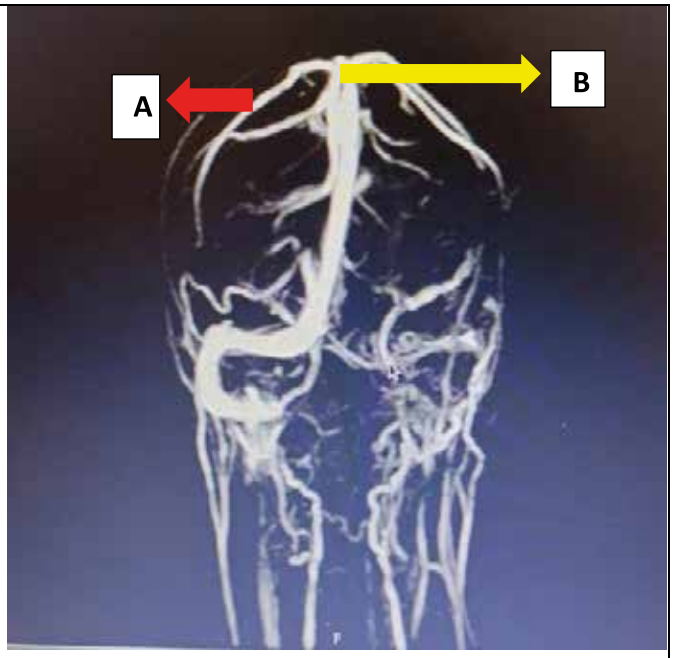

Figure 2 - MRV brain showed right cerebral venous (vein of Trolard) thrombosis (A) with extension into the draining segment of superior sagittal sinus (B).

She was immediately managed with anticoagulation, antiepileptic medication, iron replacement and physiotherapy. She was given injection low molecular weight heparin (LMWH) 40mg subcutaneously BD for first three days followed by tablet rivaroxaban 15mg BD for 21 days then 20mg OD and tablet levetiracetam 500mg BD. For anemia she was given intravenous iron and parenteral B12 replacement during hospital stay and advised to continue oral supplements at home.

Remarkable improvement was seen with complete reversal of neurological deficits by the second day of admission due to early diagnosis and timely administration of anticoagulation.

On follow up visit at three months, she had no residual deficit, anemia had improved and MRI and MRV brain showed resolution of the thrombosis. Therefore, anticoagulation was discontinued after three months.

DISCUSSION

CVST is a multifactorial illness affecting the venous segment of the neurovascular system. The clinical presentation is often ambiguous, which delays diagnosis. Neurologic symptoms can range from headache (being the most common presenting symptom), vomiting, altered sensorium to seizures. Neonates are more prone to experience seizures as a symptom of CVST, but older children and adults are more likely to experience headache, vomiting, and altered mental status.[1,2]

Up to 80% of the patients have identifiable predisposing conditions either genetic or acquired.[1,3,4] Table 2 highlights the factors which may attribute to the development of CVST. However, in approximately 20% of cases no underlying risk factor is identifed.[1,4]

Females who use contraception and have a hereditary hemostatic system problem have a 20-fold greater risk of CVST. Venous thrombosis risk increases fourfold during puberty and pregnancy. When it comes to venous thrombosis, women under 40 are twice as likely to experience it as compared to arterial infarcts.[1]

A few uncommon associations of CVST have been observed with viral illnesses, particularly Hepatitis C virus and SARSCoV-2 infection.[3, 4] A case report

documented a rare association between Hepatitis C virus and CVST.[4] In the recent COVID-19 pandemic era, several cases of encephalitis and CVST were reported, especially in patients presenting with headache, delirium, seizures, focal neurological deficit; without any prior respiratory symptoms of SARS CoV-2 infection.[3]

Anemia affects 76% of female patients with CVST, with microcytic hypochromic anemia accounting for 66% of these cases.1,2,5,6 At times more than one cause can be found in an individual patient.4 The patient in our instance had mixed anemia, which contributed to the development of CVST. Table 2 summarizes the causes and risk factors of CVST.

Table 2: CAUSES / RISK FACTORS OF CVST

1.Infection	• CNS
	• Ear, nose, throat and neck
	• Systemic
2.Inflammatory diseases	• SLE
	• IBD
	• Wegener's disease
3.Malignancy	• CNS
	• Hematologic
4.Hematologic conditions	• Prothrombotic states (genetic or acquired)
	• Polycythemia, thrombocytosis
	• Severe anemia including Paroxysmal nocturnal hemoglobinuria
5.Other causes	• Pregnancy and Puerperium
	• Dehydration
	• Drugs (oral contraceptives, HRT, corticosteroids etc.)
	• Head Trauma

In adults there are very few documented cases of CVST secondary to iron deficiency anemia, more have been reported in children. [2, 6] A case-control study reported a prevalence of 27% of CVST secondary to IDA. Anemia is more likely to result in CVST in men rather than in women. Men are also more likely to have infections or recent surgery among other risk factors that contribute to anemia. It was also proposed that the reduced incidence of anemia with CVST in women could be related to the usage of OCP. But a case-control analysis has demonstrated that this is not an implausible explanation.[6]

The precise mechanism by which IDA predisposes to thrombosis is not known but it is proposed that secondary thrombocytosis, hypercoagulability and venous stasis may play a role in the thrombus formation.[5,6] Matlik HN et al reported a case of a 15-year-old adolescent girl presenting with persistent headache associated with vomiting and dizziness. She had significant pallor, moderate dehydration but no neurological deficits. During hospital stay she developed papilledema secondary to raised ICP. Investigations revealed IDA with Hb 7.7 g/dL. MRV showed extensive thrombus in the straight and left transverse sinus extending to the left sigmoid sinus and internal jugular vein. She was admitted to intensive care unit. Upon diagnosis of CVST, LMWH was started along with simple analgesics, IV hydration, oral iron supplements and acetazolamide of raised ICP. She improved clinically and was discharged on the fifth day. Anticoagulation was given for three months.[2] Bibi A et al reports a 63-year-old vegetarian woman admitted with aphasia, right hemiparesis, confusion, and an abrupt onset of headache. A left lateral temporal lobe venous infarction with hemorrhage and thrombosis of the left transverse sinus, sigmoid sinus, jugular bulb, and left vein of Labbe was identified on brain imaging. Laboratory investigations showed severe hypochromic microcytic anemia with initial hemoglobin of 66 g/L and

MCV 57.8 fl. She was managed with infusion of unfractionated heparin, followed by warfarin for six months duration. Anemia was treated with blood transfusion followed by oral iron supplementation.[6]

Available literature shows that the documented cases of CVST secondary to anemia were treated with stabilization and symptomatic care, including anticonvulsants, correction of anemia and anticoagulation as per standard guidelines. [5,6,7,8] The same approach was followed in our case.

Heparin is the recommended anticoagulant during the acute phase of CVST (LMWH over UFH), followed by warfarin for three to 12 months while keeping the international normalized ratio (INR) within the desired therapeutic range, i.e. between 2.0 and 3.0.[7-10] More recently, direct oral anticoagulants have been utilized with encouraging results to control CVST. [8,11] ACTION-CVT, a large multicenter international retrospective study showed that treatment with direct oral anticoagulatants (DOACS) was linked to a lower risk of major bleeding events, particularly intracranial bleeding, but a similar risk of recurrent venous thrombosis and rate of partial/complete recanalization when compared to warfarin.[10]

The results of RESPECT-CVT, a randomized clinical trial showed that dabigatran (a DOAC) and warfarin were equally safe and effective.[9] This supports data from other retrospective studies. Consequently, DOACs are being used more frequently to treat CVST.[9] Anticoagulation therapy has demonstrated superior results compared to other treatment modalities, which are generally reserved for severe cases.[12] One such case was reported of a 19-year-old female. She had a history of psychiatric illness, had lost to follow up and was not on any current treatment. She was brought to hospital unconscious, later on developed status epilepticus. After extensive evaluation, she was diagnosed with CVST on a background of severe IDA due to heavy menstrual bleed. She was intubated immediately and given anti-seizure drugs. To build her hemoglobin she needed several blood transfusions. Her superior sagittal sinus was thrombosed, so a mechanical thrombectomy was performed. After which, recanalization was accomplished. She remained in the critical care unit for three weeks, where she was closely observed, underwent neurologic testing and was given continuous intravenous heparin infusion. Serial brain imaging with MRI revealed no additional thrombosis or interval changes. Even though her condition improved neurologically, she started showing behavioral changes. She was discharged in a stable condition on oral anticoagulation and advised to follow up with a hematologist.[12]

CONCLUSION

A high index of suspicion of CVST should be kept especially in young female patients with anemia, presenting with headache and focal neurological deficit followed by seizures. Anemia may be the prime contributing factor to CVST. Early commencement of anticoagulation along with correction of underlying cause, anemia in this case, leads to better prognosis.

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All the authors have approved the final version of the article and agree to be accountable for all aspects of the work.