E-ISSN:2454-9894 P-ISSN: 2454-9886
International Archives of
BioMedical and Clinical Research
(An Official Publication of "Ibn Sina Academy of Medieval Medicine & Sciences")
WWW.IABCR.ORG

Section Medicine | Original Article

# Association of Anemia with Cerebral Venous Thrombosis in Puerperium and its Pattern of Recovery

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## ABSTRACT

***Background:*** *Anemia is often considered to be a risk factor for cerebral venous thrombosis (CVT). We investigated the association between anemia and CVT.*

***Methods:*** *42 postpartum /puerperal females were studied retrospectively for various factors like anemia, conscious level at admission, place of delivery (home or hospital) and their neurological sequel was measured at the time of discharge. Platelets counts were also noted (to rule out thrombocytosis). Anemia was defined according to World Health Organization criteria: non- pregnant women hemoglobin < 7.5 gm/dl, pregnant women < 6.9gm/dl. Modified Rankin Score (mRS) was taken as a scale for recovery.*

***Results****: Patients with CVT were younger (mean age 28). Anemia was more frequent in 32.7%. Hemoglobin as a continuous variable was inversely associated with CVT. Platelets counts, BT CT were normal hence no thrombocytosis was seen. No gross increase in WBC count was noted indicating absence of sepsis (puerperal). Outcome was favorable in 83% patients. N=4 (7%) patients died.*

***Conclusions****: We found a significant association of severe anemia and CVT in patients of CVT of non-infectious origin, although the exact mechanism leading to hypercoagulability remains unclear and had poor prognosis.*

***Key words****: cerebral venous thrombosis (CVT), anemia, IDA, neurological deficit*

**Received:** 19.05.17 | **Accepted**:21.06.17

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**How to cite this article**: Gupta NK, Chhaparwal JK, Kanwaria DK, Meena RR, Nayak KC. Association of Anemia with Cerebral Venous Thrombosis in Puerperium and its Pattern of Recovery. Int Arch BioMed Clin Res. 2017;3(3):60-63.DOI:10.21276/iabcr.2017.3.3.16

**Source of Support:** Nil, **Conflict of Interest:** None



## INTRODUCTION

CVT has a variable clinical presentation. It has been found that two mechanisms may principally lead to the clinical features of CVT (1). The first is the thrombosis of cerebral veins or dural sinus leading to cerebral parenchymal lesions or dysfunction. The second being the occlusion of the dural sinus resulting in decreased cerebral spinal fluid (CSF) absorption and elevated intracranial pressure (ICP).

Clinical symptoms of CVT may simulate neurological diseases like stroke, brain tumor and encephalopathy, the most frequent being headache.[1] Diagnostic imaging by MRI in combination with MRV is the single most sensitive technique for demonstrating CVT.[2] Non-contrast CT Scan -Direct Findings includes Dense Cord Sign, Dense Dural Sinuses, Dense Jugular Vein, Dense Triangle or Delta Sign.

The most frequent location of CVT includes the superior sagittal sinus (62%) followed by lateral or transverse sinuses (41-45%).

Most patients with CVT have a good prognosis. 5% of patient died in acute phase due to neurologic sequelae most commonly brain herniation whereas 10% of patients die

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| DOI: 10.21276/iabcr.2017.3.3.16 | |

secondary to long term sequelae. A poor prognosis is associated with deep CVT as well as altered mental status. The recurrence of CVT is relatively uncommon.[3] Treatment for CVT includes antithrombotic therapy as well as symptomatic treatments.

CVT is multifactorial and has been associated with the following: inherited hypercoagulable state, pregnancy, puerperium, cancer, intracranial or systemic infections, vasculitis, oral contraceptives and substance abuse.[4]

## METHODS

Cases were female adult patients with CVT. The age group of these selected subjects was between 18- 35 years of age. Data on clinical manifestations, imaging and outcome were recorded with a standardized format. We extracted hemoglobin concentration and mean corpuscular volume (MCV).

All laboratory measurements were done as a part of routine diagnostic work up within 48 hours of admission. Blood was collected into vacuum tubes containing 0.106 mmol/L trisodium citrate and processed within 4 hours. The final concentration of hemoglobin was multiplied by a factor of 1.1 to adjust for the dilution by the trisodium citrate.

**Definition of Anemia**: We used the World Health Organization definitions for anemia: Non-pregnant women hemoglobin < 7.5 gm/dl, pregnant women < 6.9gm/dl. Anemia is categorized as microcytic (MCV< 80fl), normocytic (MCV 80-100fl) or macrocytic anemia (MCV >100). Increased hemoglobin was defined as > 10.2 gm/dl. We excluded patients of malignancy, recent infection.

| WHO classification of Anemia | | | |
|---|---|---|---|
| | Mild(gm/dl | Moderate | Severe |
| **Non-Pregnant Females** | 11 - 11.9 | 8 - 10.9 | < 8 |
| **Pregnant Females** | 10 - 10.9 | 7 - 9.9 | < 7 |

**Table 1: Definition of Anemia and pathologic data.**

| | |
|---|---|
| **Severe Anemia** | **Hb < 7 gm/dl** |
| **Macrocytic** | **MCV >96 fl** |
| **Microcytic** | **MCV <81 fl** |
| **Hypochromic** | **MCH <26 pg** |
| **Hypechromic** | **MCH >33 pg** |
| | |
| **Thrombocytes** | |
| **Thrombocytosis** | **Thrombocytes > 470 x $10^9$ /l$^{14}$** |
| **Thrombocytopenia** | **Thrombocytes < 140 x $10^9$ /l$^{14}$** |
| | |
| **Leucocytes** | |
| **Leucocytosis** | **Leucocytes > 11x $10^9$ /l$^{14}$** |
| **Leucopenia** | **Leucocytes < 4 x$10^9$ /l$^{14}$** |

Prognosis and recovery pattern was done by Modified Rankin Score (mRS).[14]

**Table: 2 Correlation of Anemia with outcome (pattern of recovery)**

| Anaemia | Pattern of Recovery |
|---|---|
| **Mild Anemia (>10.0gm/dl <13 gm/dl)** | Full recovery (78%) |
| **Moderate Anemia (>7 gm/dl < 9.9gm/dl)** | Depend on other for routine activities (10%) |
| **Severe Anemia (<6.9gm/dl )** | Fatal outcome (4 death) (7%) |

## RESULTS

In the present study, the main predisposing factors were anemia, dehydration and sepsis. None of the patients were taking oral contraceptives. Most of the patients nearly about 72% had hemoglobin less than 6.9 gm/dl and had fatal outcome in whom 4 patients died and other 24% had to depend on others for their routine activities.

Other patients who had their hemoglobin more than 6.7gm/dl but less than 11gm/dl recovered well with 4 recovering completely and 2 patients being independent but having slight deficit.

After adjustment for potential confounders (age, mode of delivery) anemia was significantly associated with CVT. Similarly, hemoglobin concentration was inversely associated with CVT risk. Patients who got delivered at home had bad prognosis then who got delivered in the hospital.

Outcome was favorable in 83% patients. At the end of follow up 32 patients (78%) had complete recovery (mRS 0 -1), 2 (5%) had partial recovery and 4 (10%) were dependent (mRS 3 -5). N=4 (7%) patient died.

## DISCUSSION

Relationship between anemia and CVT.

Low hemoglobin causes poor oxygenation. As a result, anemic hypoxia could precipitate situations of increased metabolic stress predominantly in susceptible areas of the brain like basal ganglia and thalamus due to end arterial supply.

Thrombopoiesis is significantly regulated by iron[5], as normal quantity of iron is fundamental not only to maintain platelet production but also to prevent thrombocytosis. Thus, iron deficiency occasionally leads to thrombocytosis, which is associated with a hypercoagulable state. However, few cases of thrombocytopenia have been reported.[6] When iron deprivation occurs, it first leads to thrombocytosis; once the iron deficiency is severe enough to deplete iron, thrombocytopenia occurs.[5]

Iron deficiency may also induce a hypercoagulable state by altering pattern of blood flow within the vessels due to decreased deformability and increased viscosity i.e. thickness of microcytic RBC.[7]

Hypercoagulability, hemodynamic changes (either stasis or turbulence), and endothelial injury play important role in the thrombosis formation, according to Virchow's triad. Among these, hypercoagulability and stagnant flow predominate in thrombus formation in IDA.[8] Although anemia causes

increased arterial blood flow velocity[9], it contributes to stasis in veins as a result of reduced deformability of microcytic RBC, which further leads to increased viscosity.[7] Intravascular thrombogenesis also caused by acute bleeding, as it augments platelet adhesiveness and reduces fibrinolytic activity.[10]

Even though this report did not specify the type of anemia and did not include the systemic analysis of iron metabolism, severe anemia was microcytic in 63% of cases. Hence, in most cases, iron deficiency anemia can be assumed.[11]

Recurrence of CVT could be significantly prevented by supplementation therapy for Iron deficiency. Comprehensive treatment for IDA is required, as in the acute phase of CVT, anemia is frequently noticed as a relatively low hemoglobin (Hb) concentration.[12]

The primary cause of CVT influenced by prothrombotic state of pregnancy itself often in the setting of dehydration or an underlying predisposition for thrombophillia. The physiologic changes during pregnancy that may lead to arterio-venous thromboembolism includes decrease in circulatory anti-thrombotic factors, venous stasis or sudden reduction in blood volume after delivery. The activity of majority of coagulation factors (I, II, VIII, IX, X, XII) increases during pregnancy.

In this study severe anemia was independently associated with CVT which might be interpreted as a higher dependence of hypercoagulability on the hemoglobin and hematocrit level rather than on the extent of thrombocytosis. Nevertheless, the exact mechanisms leading to changes in coagulation are not yet known.

**CT Scan findings (Non-contrast) - Direct Findings**

1. Dense Cord Sign: This represents a thrombosed cortical vein.

2. Dense Triangle or Delta Sign: This represents an acute thrombosis of the posterior superior sagittal sinus. In the first two weeks, thrombotic blood is usually hyper dense on an unenhanced CT scan compared to the brain parenchyma; therefore, these signs are usually present during the first two weeks only. After two weeks, a thrombus will become isointense to brain parenchyma and therefore will only be visible on a post contrast CT.

**Noncontrast CT Scan - Indirect Findings**

1. Non-hemorrhagic Infarcts: This is the most common indirect finding in CVT and can be cortical, sub cortical or deep. Multiple infarcts which do not follow any single arterial territory should raise the suspicion of CVT. Bilateral thalamic infarcts are highly suggestive of deep venous system thrombosis.[15] Bilateral parasagittal hypodense lesions on CT are a common finding in venous thrombosis of the superior sagittal sinus.[16]

2. Hemorrhagic Venous Infarcts: Venous backlog leads to infarcts which are often hemorrhagic. These are present in 10% to 50% of cases with CVT.

3. Multifocal Hemorrhages: Multiple areas of hemorrhages are again due to venous backlog and subsequent venous bleeding. These are present in 2% to 10% of cases with CVT.[15]

**Post contrast CT Scan Findings -**

Empty Delta Sign: This is the most commonly seen direct finding of CVT on CT imaging and is present in 10% to 30% of cases with CVT.[15] This is a triangular filling defect and represents opacification of collateral veins in the superior sagittal sinus wall with non-opacification of the clot within the sinus. Due to the orientation of the superior sagittal sinus and the usually employed axial plane of imaging it can be seen only in the posterior third of the superior sagittal sinus. A false positive empty delta sign can be produced by fenestration or septa within the superior sagittal sinus. The most frequent location of CVT includes the superior sagittal sinus (62%) followed by lateral or transverse sinuses (41-45%).

## CONCLUSION

In conclusion, we found a significant association of severe anemia and CVT in patients of CVT of non-infectious origin, although the exact mechanism leading to hypercoagulability remains unclear and had poor prognosis.

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