Impact of Anemia on Cerebral Venous Thrombosis Patients Compared to Arterial Stroke

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ABSTRACT:

BACKGROUND:

Cerebral venous thrombosis (CVT) is a condition where a thrombotic event involves cerebral venous sinuses of varied temporal evolution. It causes stroke with incidence of ≈1.3 per 100000 especially in young female. Many - risk factors had attributed in its etiology assuming, anemia, as one of these factor, - based on case reports and case series.

AIM OF STUDY:

To assess the impact of anaemia on cerebral venous thrombosis (CVT) in comparison with arterial stroke

PATIENTS AND METHODS:

A case control prospective study performed at Al-Imamain Al-Kadhimain Medical City throughout the period from December-2017 to December-2019. It included 42 randomly selected cerebral venous thrombosis (CVT) patients who compared with another 60 patients with arterial stroke as control patient group -Both groups were offered complete blood count (CBC) within 48 hours as part of routine investigation. Those discovered to have anemia were categorized according to severity using WHO definition in both groups as well as their mean corpuscular volume (MCV). Statistical analyses performed to define the relationship between anemia, microcytosis and CVT diagnosis. Kaplan-Meier curve used to assess the survival of patients with CVT during the early outcome period of 14 days.

RESULTS:

Mean patients Hb was 11.05±3.11mg/dl versus 13.62±3.73 mg/dl in control group (p value < 0.001) with lower MCV (74.88±12.85 fl versus86.43±9.02 fl) (p value < 0.001). Severe anemia and severe microcytosis were associated significantly with CVT (OR= 13.5, 95% CI= 2.47-73.71, p= 0.001), (OR=2.87, 95%CI=2.17-3.8, p<0.001) respectively independently but not as such in combination with other confirmed other risk factors like age and gender. It is observed that mean duration of death was 8.5 days in CVT patients with anamia (p value 0.227). All dead cases had severe anemia.

CONCLUSION:

There is inverse association between severity of anemia, microcytosis with CVT incidence, which may be considered as separate risk factors. The presence of anemia in CVT patient may result in - poor outcome and increasing early mortality rate.

KEY WORDS: Cerebral venous thrombosis, anaemia and stroke.

INTRODUCTION:

Cerebral venous thrombosis or sino-venous thrombosis-is a condition which involves cerebral venous sinuses and veins together or independent of each other with thrombotic event of varied temporal evolution [1,2].

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Cerebral venous thrombosis (CVT) is a rare cause of stroke with an incidence of ≈1.3 per 100000 among adults [3, 4]. CVT mainly affects young to middle aged adults and children, and >90% are <60 years [5].

It is regarded as a continuing process of imbalance between prothrombotic and thrombolytic processes [6,7].

The impact of CVT on the brain is wide spectrum, ranging from completely normal parenchyma to brain oedema and/or haemorrhage [8, 9].

Multiple mechanisms relate to the extent of neuronal injury in CVT including; dural sinus pressure, venous flow obstruction, collateralization of venous channels, rate of occlusion, development of cytotoxic and vasogenic oedema, recanalization of venous channels and development of infarction and haemorrhage [8].

Female sex is one of the major risk factors for CVT, as cases in women to men ratio 3 to 1 , 65 % percent of identifiable causes of CVT in women were related to a risk factor unique to women, including oral contraceptives, pregnancy, the puerperium, and hormone therapy[10]. Transient risks and triggers are frequently considered to be related to a temporary condition, such as-central nervous system or ear/sinus/mouth/ face infections, exposure to drugs (e.g., oral contraceptives, steroids, oncology treatments), head trauma, or procedures [11]. Chronic triggers may include hereditary or acquired thrombophilias, haematological disorders (e.g., paroxysmal noctornal hemoglobinurea, Iron deficiency anemia, polycythemia, thrombocytopenia in setting of warfarin or heparin use), systemic diseases (systemic lupus erythematosus, Behcjet disease, sarcoidosis, inflammatory bowel disease) [5, 10].

Anaemia is estimated to affect 1.6 billion people. The highest prevalence is found in preschool-age children (47.4%), followed by pregnant females (41.8%), non-pregnant females (30.2%), school-age children (25.4%), and males (12.7%)[12].

It is defined in non-pregnant women as haemoglobin < (12 g/dl), pregnant women < (11 g/dl), and in men < (13 g/dl). Severe anemia is denotes to haemoglobin < (9 g/ dl) for men and non-pregnant women or haemoglobin < (7.7 g/dl) for pregnant women [13] [14].

Several mechanisms have been postulated for the association of quantitative and qualitative erythrocyte defects with thrombosis [15].

First, in anemic state, hypoxia- may affect the interaction between erythrocytes and endothelium and therefore increase the risk for thrombosis [16].

Second, iron deficiency, (the most common type of anemia globally)[17], has been linked to thrombosis secondary to reduced inhibition of thrombopoiesis and subsequent reactive thrombocytosis[18].

Third, anemia may be accompanied by altered erythrocyte morphology (e.g., sickle cell disease (SCD) -) that increases blood viscosity [19], with elevated circulating prothrombin fragment, indicating that erythrocytes in certain settings may potentiate thrombin generation [20, 21]. Also, haemoglobin and adenosine diphosphate released from haemolysed erythrocytes may enhance thrombosis by promoting platelet activation and aggregation [22,23]. Last-cytokines such as tumour necrosis factor alpha, interleukin IL-6, and IL-2 may mediate the development of Venous thromboembolism in aplastic anemia[24], possibly by inducing the production of reactive oxygen species[25].

Two case control studies evaluated the relationship of anaemia with CVT; the study of **Stolz et al., 2007** found a weak, but significant association with severe anaemia, arbitrarily defined as Hb > 90 g / dl [26] and the study of **Coutinhu et al., 2015** found a significant association with anemia when the author suggested a linear inverse association between the risk of CVT and Hb concentration [27].

The aim of the study is to assess the impact of anaemia on CVT in comparison with arterial stroke.

PATIENTS AND METHODS:

It is a case control prospective study that performed at the neurology and internal medicine units of **Al-Imamain Al-Kadhimain** medical city throughout the period from December - 2017 to December - 2019 over 24 months, where random selection of CVT patients as well as arterial stroke patients as control cases were enrolled.

Forty two patients, with a diagnosis of CVT that based on clinical features, physical examination and brain MRI / MRV, had been studied as patients group were enrolled in the study.

Study already defines the exclusion criteria as the following:

1- Patients with inconclusive finding of CVT on CT scan and MRI like hypertensive hemorrhage, arterial stroke, metabolic encephalopathy and presence of space occupying lesions.
2- Those with possible underlying etiology like:
   a. Known thrombophilic condition as SLE or Familial thrombophilia.
   b. Malignancy.
   c. Chronic liver disease.
   d. Chronic kidney disease.
   e. Inflammatory bowel disease.

Another 60 patients diagnosed to have arterial stroke based on clinical picture, physical examination and brain image (CT, MRI with DWI) were also included as (diseased control) for comparison concerning the aspect of common prevalence of anemia.

For both groups (patients and controls) a detailed history revised with respect to demographical, clinical and radiological features, with special emphasis on suspected precipitating or predisposing factors such as puerperium, fever, ear pain or discharge that my suggest meningitis or otitis media, history of hypovolemia induced by fasting, diarrhea and /or vomiting within a week of admission, anemia, abortions and contraception use (weather previous or current use of contraceptive or hormonal therapy). Detailed examination of patients carried out including general physical examination for any evidence of anemia, hypovolemia, sepsis, deep vein thrombosis of leg, evidence of otitis media and detailed neurological assessment with other systems done to look for any evidence of possible etiologies.

Both groups - were offered complete blood count (CBC) within 48 hours as part of routine investigation. A 5 millilitre of venous blood sample collected into vaccum tubes containing 0.106mmol/l EDTA and processed within 4 hours. For the following laboratory measurements (platelets, white blood cell count, haemoglobin

Purpose of the study was carefully explained to the patients and an oral informed consent obtained. Regarding aphasic patient, informed consent obtained from next of kin or relative for them in cases as well as control groups.

RESULTS:

Baseline Characteristics of the study population:

Patients group age range between (19 – 60) years old while age range of controls was a (20 – 82) year old. The mean age of patients group was 38.17±11.87 years which was much lower than that of control group with a high significant difference, (p value 0.001).

Males represented 61.67% of control group, and 30.9% of patients group, with female predominance in patients group with a significant difference (p value 0.003.

Three main veins were found to be involved in thrombosis using MRI with venography. A patient can have more than one affected veins. Right lateral sinus thrombosis was the most culprit vein in 19/42 patients (45.24%) followed by superior sagittal sinus in 16/42 patients (38.1%) and finally, left lateral sinus which was reported in 12 patients (28.57%). Other various sites of thrombosis (straight, Inferior sagittal sinus, deep vein of Galen and cavernous sinus) were reported in 11/42 patients (26.19%).

Interestingly, 31/42 patients (73.81%) had single vein thrombosis, while 11/42 (26.19%) had multiple vein thrombosis where lateral sinus thrombosis comprise 11.9% for each side as single vein pathology prevalence.

Haematological Parameters: Mean Hb concentration in patients and controls was 11.05±3.11mg/dl and 13.62±3.73 mg/dl respectively with a high significant difference (p value < 0.001). In addition, MCV was much lower in patients (74.88±12.85 fl) than control (86.43±9.02 fl) with a high statistical significance (p value < 0.001).

Accordingly, anemia was more frequent among patients than control (52.38% versus 20%), with a high significant difference (p value < 0.001).

Microcytosis similarly reported in 52.38% of patients (p value < 0.001) compared with 21.67% of control, with a high significant difference (p value < 0.001).

On the other hand, no significant differences were found between the two groups regarding WBC count or platelets count (Table 1).

When anemia looks to have causal relationship with CVT, it is important to remark the pathogenesis, and it is valuable to mention that all patients with low haemoglobin level in this study were diagnosed with **iron deficiency anemia.**

Association of severity of anemia and microcytosis in cases and controls: Severe anemia was found in 18 CVT patients (41.86%) compared with only 3 control patient (5%) with a high significant difference (OR= 13.5, 95%CI= 2.47-73.71, p= 0.001). Furthermore, 20 CVT patients (47.62%) were suffering from severe microcytosis versus none of control patients with a high significant difference (OR=2.87, 95%CI=2.17-3.8, p<0.001) as shown in (Table 2).

The association between multiple risk factors: Basic characteristics and haematological parameters those with significant association with CVT were analysed in a multivariate logistic regression test as shown in (Table 3). Each of age, gender and evidence of volume loss have kept their significant association with CVT. CVT patients were younger than 50 years compared to only 13.33% of stroke patients with this age (OR=0.02), (0. 05-0.11, p<0.001). Similarly, 69.05% of CVT patients were female versus 38.33% among control patients (OR= 4.95, 95% CI=1.05-23.44, p=0.044). Finally, evidence of volume loss was reported in 21.42% of CVT patients compared with 3.33% of control patients who had such evidence (OR= 15.1, 95%= 0.4-163.38, p= 0.025). In the other hand, anemia didn't show significant association in the presence of other risk factors (p value 0.463).

Anemia as Predictor for Survival in CVT Patients: Kaplan Meier curve (Figure 1) was used to find 14 days' survival in anemic and non-anemic patients CVT. It is shown that anemia with CVT had mean duration for death of 8.5 days, but of no statistical significance (p value 0.227).

Table 1: Relationship of CBC parameters in cases and controls groups.

Variables	Cases (n=42)	Controls (n=60)	p-value
Hb, mg/dl (mean±SD)	11.05±3.11	13.62±3.73	<0.001
MCV, femtoliter (mean±SD)	74.88±12.85	86.43±9.02	<0.001
WBC×10^9/L (mean±SD)	9.9±4.04	8.58±3.9	0.101
Platelets×10^9/L (mean±SD)	296.0±127.3	277.7±132.9	0.489
Anemia No Yes	 20(47.62%) 22(52.38%)	 48(80%) 12(20%)	 <0.001
MCV Normocytic Microcytic	 20(47.62%) 22(52.38%)	 47(78.33%) 13(21.67%)	 <0.001

Table 2:Association of severity of anemia and microcytosis in both patients and control groups.

Variables	Cases (n=42)	Controls (n=60)	p-value	OR(95%CI)
Anemia Mild to moderate Severe	 4(9.3%) 18(41.86)	 9(15%) 3(5%)	 0.001	 1.0 13.5(2.47-73.71)
Microcytosis >80 fl ≤80 fl	 22(52.38%) 20(47.62%)	 60(100%) 0(0%)	 <0.001	 1.0 2.87(2.17-3.8)

Table 3: Analysis of multiple clinical, haematological risk factors in relation to CVT incidence.

Variables	p-value	OR(95%CI)
Age, years ≤50 >50	 <0.001	 1.0 0.02(0. 05-0.11)
Gender Male Female	 0.044	 1.0 4.95(1.05-23.44)
Evidence of volume loss No Yes	 0.025	 1.0 15.11(1.4-163.38)
Anemia No Yes	 0.463	 1.0 2.39(0.23-24.42)
Mean corpuscular volume Normocytic Microcytic	 0.447	 1.0 2.35(0.26-21.15)

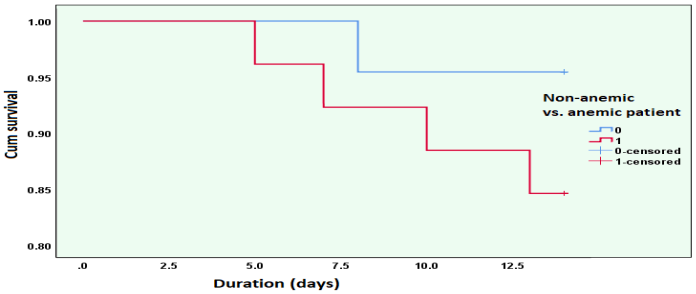

Figure 1: Kaplan-Meier curve. Mean time for survival in anemic and non-anemic CVT patients.

DISCUSSION:

In this study, the impact of anemia is assessed depending of different haematological parameters. Concerning haematological parameters, it is found that both haemoglobin level and microcytosis have a significant association with the risk of developing CVT in comparison with arterial stroke (p value < 0.001).

Similarly the severity of anemia and the presence of microcytosis are associated with prothrombotic state, whether venous or arterial (p value 0.001, <0.001 respectively).

Anemia was more frequent among CVT patients than control patients with prevalence of (52.38% versus 20%), which was mainly of microcytic type with a high significant difference (p value < 0.001).

Severe anemia was more prevalent in CVT patients compared with control cases with a high significant difference (OR= 13.5, 95% CI=2.47-73.71, p=0.001). Furthermore, severe microcytosis was reported significantly in CVT patient with a high significant difference (OR=2.87, 95%CI=2.17-3.8, p<0.001).

The impact of RBC shape and shear stress on blood viscosity confer that the presence of high shear rate as in (arterial territory) and transient deformation of RBC will reduce blood viscosity inside arteries, while conversely at (venous territory) there is low shear rate and slow movement of blood coupled with the discoid RBC morphology will allow electrostatic interaction to promote RBC aggregation in to stacked “rouleaux” structures which increase blood viscosity[19,28,29,30].

Increased blood viscosity is an established risk factor for thrombosis[31]. RBCs are the primary determinants of blood viscosity due to their discoid shape, deformability, intrinsic viscoelastic properties, and fibrinogen-binding ability, [32,33].

Intact RBCs can directly adhere to the endothelium or subendothelial matrix or bind through interactions with other blood proteins and/or cells, including neutrophils and platelets [34,35]. In straight vessels with arterial shear rates, RBCs promote platelet margination, which can enrich the near-wall platelet concentration three to fivefold [36, 37, and 38]. In silico simulations suggest margination increases platelet–vessel wall interactions and enhances platelet deposition on thrombi by reducing the distance between flowing platelets and the thrombus and increasing the frequency and duration of these interactions[39,40], haemoglobin and ADP released from haemolysed or damaged RBCs biochemically enhance platelet activation and aggregation[41,23].

Just like Coutinho et al. 2011 when the mean haemoglobin concentration was lower in cases than in controls (P<0.001). Severe anemia was present in 2.6% of cases versus none in the controls (absolute difference, 2.6%; 95% CI, 1.0 to 6.6). The study concluded that CVT was associated with anemia significantly with a linear inverse association between Hb concentration and the risk of CVT [27].

In Guptab NKb et,al. 2017 anemia was frequent(32.7%) in 42 postpartum/puerperal females. After adjustment for potential confounders, anemia was associated with CVT significantly. Similarly Hb concentration was inversely associated with CVT risk. Platelet count and WBC count was not related to CVT just like in this study [42].

Basic characteristics and haematological parameters that showed a significant association with CVT analysed to assess their effect on patients group together. Each of age, gender and evidence of volume loss have kept their significant association with CVT, (p values < 0.001, 0.04, and 0.025 respectively).

In the other hand, anemia seems to be affected by other confounders (p value 0.471, 0.463 respectively) and seems to be dependant risk factor. Meaning that the presence of such strong predisposing factors (age, sex, hypovolemia) predominate the effect of anemia despite their significant association when considered solely, suggesting that the occurrence of anemia in patients add absolute risk for CVT to the baseline risks. Some studies have found that oral contraceptive pills decrease the risk of anemia, which could result in a lower prevalence of anemia among women with CVT [43,44].

The study of Stolz et al,. 2007 found a weak, yet significant association of severe anemia, arbitrarily defined as Hb < 90 g/l, and CVT after adjustment for potential confounders by logistic regression. A shortcoming of this study is the lack of a systematic study of iron metabolism, so that they can not specify the type of anemia other than based on the results of the blood count. However, severe anemia was associated with thrombocytosis in 81% and was microcytic in 63% of cases so that in most cases an iron deficiency anemia can be assumed but not assured [26].

Similar to the former study, Gupta NK et al. 2017 study showed that severe anemia was independently associated with CVT which might be interpreted as a higher dependence of hypercoagulability on the haemoglobin and haematocrit level rather than on the extent of thrombocytosis. [42].

There is considerable variation in the mortality rate associated with this condition, may be influenced by the patient's demographics and the pathological conditions leading to cerebral venous thrombosis [45]. In this study, we tried to assess the anemia as a predictor of survival within14 days of presentation of CVT. Death rate was (9.5 %). For anemic patients, mean duration for death was 8.5 days (95%CI= 5.0-13.0) while there was non-limited duration for non-anemic patient. It is worthy to know that all dead cases had severe anemia, suggesting that anemia associated with poor prognosis and outcome. One limitation encountered here when the screen of thrombophilia wasn't possible in dead cases.

Similarly, Gupta NK et al,. 2017 concluded that severe anemia associated with CVT and with poorer prognosis, and they suggest that supplementation therapy for iron deficiency significantly prevent recurrence of CVT[42].

CONCLUSION:

There is an inverse association between severity of anemia, microcytosis with CVT incidence, which may be considered as separate risk factors. The presence of anemia in CVT patient may result in poor outcome and increasing early mortality rate.

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