Research Article

Elevated factor VIII level in cerebral venous thrombosis: a case-control study

Bhavin Bhagwan, Manesh Pillay, Clara-Maria Schutte, Andries Masenge, Mandisa Kakaza

Department of Neurology, Steve Biko Academic Hospital, Pretoria, South Africa

*Corresponding Author: *bhavin.bhagwan777@gmail.com*

ABSTRACT

Background: Cerebral venous thrombosis (CVT) is an uncommon disorder accounting for approximately 1% of strokes worldwide There is a paucity of data regarding the association between an elevated factor VIII level and cerebral venous thrombosis (CVT).

Methods: From June 2015 to January 2022, patients with confirmed CVT on neuroimaging were identified at two public hospitals in South Africa. Their clinical presentation, radiological characteristics of thrombosis, and risk factors for CVT were analysed. Age-, sex-, and HIV status-matched controls were recruited. Factor VIII levels were analysed in patients with CVT and in controls.

Results: The study included 26 patients with CVT and 52 controls. The mean age was 40.3 and 41.4 years for the patients and controls, respectively. In the study group, 73% were females. An elevated factor VIII level (>150 IU/dL) was the most common risk factor, identified in 61.5% (16/26) of patients with CVT. The mean factor VIII level was significantly higher in patients with CVT compared to controls (200.1 vs 156.9, p = 0.017). An elevated factor VIII level (>200 IU/dL) increased the risk of CVT four-fold (age- and sex-adjusted OR: 4.437, 95% CI: 1.435–13.723, p = 0.009).

Conclusions: An elevated factor VIII level is a common risk factor for CVT; hence, investigation thereof should be included in the aetiological work-up. This study suggests that a higher cut-off value for factor VIII level increases the strength of the association with CVT.

Keywords: Elevated factor VIII, cerebral venous thrombosis, risk factor, South Africa, HIV

INTRODUCTION

Cerebral venous thrombosis (CVT) is an uncommon yet serious cerebrovascular disorder, accounting for approximately 1% of strokes worldwide.(1) This form of venous thrombosis is marked by the clotting of blood in cerebral veins or dural venous sinuses. The list of risk factors that predispose to CVT is extensive, including pregnancy and the puerperium, prothrombotic states, and infection. In certain cases, dual or multifactorial causes are found, yet in 12.5% of cases, no underlying risk factor is identified.(2)

Factor VIII is a glycoprotein that plays an important role in the intrinsic pathway of blood coagulation: it functions as a cofactor for activated factor IX.(3) Plasma factor VIII levels are influenced by a combination of genetic and acquired factors, including ABO blood group and von Willebrand Factor (vWF) level.(4) An elevated factor VIII level is now an established risk factor for deep vein thrombosis (DVT) and pulmonary embolism (PE), the common forms of venous thromboembolism (VTE).(5–10) The pathophysiological pathway through which an elevated factor VIII level causes a thrombophilic effect is uncertain. Theories include a direct factor VIII-mediated augmentation of thrombin generation or inducing activated protein C resistance.(10–13)

There is a paucity of data regarding the association between an elevated factor VIII level and CVT. The association has been assessed previously in a few control studies, but sample sizes have been small.(14–17) To our

knowledge, there is no published data from South Africa evaluating factor VIII levels in patients with CVT.

The aim of this study was to investigate the association of plasma factor VIII level with CVT in patients admitted to two public hospitals in Pretoria, South Africa.

METHODS

Study design and patient selection

This was a case-control study, with the use of an age-matched, sex-matched and HIV status-matched control group in a 1: 2 ratio (CVT patients: controls).

CVT patient group (Sample size = 26)

Patients who presented with CVT were identified at Steve Biko Academic Hospital and Kalafong Provincial Tertiary Hospital in Pretoria, South Africa from June 2015 to January 2022. A total of 42 patients were identified: 4 had demised; 12 were lost to follow up and unable to be contacted telephonically. Thus 26 patients were contacted telephonically and recruited. Patients were age 18 years or older, and CVT was confirmed on neuro-imaging either by brain computed tomography (CT) and/or CT venography, or by brain magnetic resonance imaging (MRI) and/or MR venography protocols. Written informed consent was obtained from all study participants and the study was approved by the University of Pretoria Faculty of Health Sciences Research Ethics Committee.

Control Group (Sample size = 52):

Age (within 5 years), sex and HIV status-matched outpatient-based controls, with no history of thrombosis, were identified from the neurology outpatient departments at Steve Biko Academic Hospital and Kalafong Provincial Tertiary Hospital, in a 1:2 ratio (CVT patients: controls). Recruitment commenced on 15 November 2022 and concluded on 7 July 2023. Only participants without a history of previous thrombosis, current pregnancy, recent surgery (within 3 months), known malignancy, chronic inflammatory disease, current or recent use of anticoagulant treatment (within 3 months) were recruited as controls. Written informed consent was obtained from all control participants.

MEASUREMENTS

The data on patient demographics, clinical presentation, thrombus location, episode of previous thrombosis, family history of thrombosis, risk factors for CVT, duration of anticoagulation treatment and dates of all thrombotic events was recorded.

The following risk factors were evaluated: genetic (protein C deficiency, protein S deficiency, antithrombin III deficiency, factor V Leiden mutation, prothrombin G20210A mutation, JAK-2 mutation) and acquired (pregnancy/puerperium, hyperhomocysteinaemia, antiphospholipid syndrome) prothrombotic states; inflammatory or autoimmune diseases (inflammatory bowel disease, Behçet's disease, systemic lupus erythematosus, granulomatosis with polyangiitis, sarcoidosis); haematological disorders (polycythaemia, thrombocythaemia, thrombotic thrombocytopenic purpura, paroxysmal nocturnal haemoglobinuria); oral contraceptive use (at time of occurrence of CVT); infection-related (HIV, meningitis, local head or face infection, COVID-19 infection or vaccine within 3 months prior to CVT event); malignancy (central nervous system (CNS) tumours, systemic malignancies, solid tumours outside the CNS); and mechanical event (head trauma, neurosurgical procedures, jugular vein catheterization).

Plasma factor VIII level was assessed from each participant (at the earliest more than 3 months after the thrombotic event in the CVT group) at the National Health Laboratory Service, at Steve Biko Academic Hospital. The coagulation instrument used for the calculation of the plasma factor VIII level was the Sysmex CS-2500. The method was haemostasis analysis using photo-optical clot detection. An upper limit cut-off value of 150 IU/dL was used for the plasma factor VIII level, in accordance with international laboratories and literature.(18)

STATISTICAL ANALYSIS

The data collected was entered into Microsoft Office 2019. IBM SPSS Statistics version 28 was used to perform the analysis. To describe the characteristics of the CVT patient and control groups, frequency tables (counts and percentages) for categorical variables were calculated; means and standard deviations were presented for age. Descriptive statistics (means, standard deviations) of the factor VIII level were determined for the patients with CVT and the control group. The t-test was used to assess whether the mean factor VIII level differed between the CVT and control patients, whether the mean factor VIII level differed between patients with single and multiple sinus involvement, and whether the mean factor VIII level differed between patients using oral anticoagulation and patients not using oral anticoagulation.

RESULTS

Baseline characteristics, clinical presentation, neuro-imaging features and risk factors of patients with CVT.

The study group consisted of 26 patients (19 females; 7 males); the mean age was 40 years with age range of 18 to 71 years. Baseline characteristics, clinical presentation, cerebral venous sinuses involved and risk factors identified in the CVT case group are depicted in Table 1. The most common clinical presentations were isolated intracranial hypertension in 34.6% (9/26), encephalopathy in 30.8% (8/26), and focal syndrome in 26.9% (7/26). The most frequently involved cerebral venous sinuses were the superior sagittal sinus in 65.4% (17/26), left transverse sinus in 57.7% (15/26) and left sigmoid sinus in 42.3% (11/26).

Table 1: Baseline characteristics, clinical presentation, cerebral venous sinuses involved and risk factors of patients with CVT

Patient Number	Age / Sex	Clinical Presentation	Cerebral Venous Sinuses involved on Neuro-imaging	Number of Sinuses involved	Traditional Risk Factors	Factor VIII Level (IU/dL)
1	45 / F	Focal Syndrome	SSS, Left TS, Left SS, Left IJV	4	Oral Contraceptive	303.9
2	32 / F	Focal Syndrome	SSS, Right TS, Right SS, Right IJV	4	Pregnancy	174.6
3	43 / M	Focal Syndrome	Left TS, Left SS, Left IJV	3	Genetic Thrombophilia (JAK-2 mutation)	149.4
4	71 / F	Isolated Intracranial HPT	Left TS, Left SS, Left IJV	3	-	267.8
5	18 / F	Focal Syndrome	SSS	1	Antiphospholipid Syndrome	453.8
6	20 / F	Encephalopathy	SSS, Bilateral TS, Right SS	4	-	154.4
7	27 / F	Isolated Intracranial HPT	SSS, Bilateral TS, Straight Sinus	4	Oral Contraceptive	224.5
8	35 / F	Encephalopathy	Left TS	1	Pregnancy	149.2
9	40 / F	Encephalopathy	SSS, Bilateral TS, Bilateral SS	5	Puerperium Genetic Thrombophilia (Prothrombin G20210A mutation)	206.4
10	52 / M	Isolated Intracranial HPT	SSS, Left TS	2	Meningitis	221.8
11	49 / F	Encephalopathy	SSS, Bilateral TS, Bilateral SS	5	Oral Contraceptive	127.8
12	44 / F	Cavernous Sinus Syndrome	Right CS	1	Local head / face infection	171.1
13	21 / F	Isolated Intracranial HPT	SSS	1	HIV	83.3
14	34 / F	Isolated Intracranial HPT	SSS, Bilateral TS	3	Oral Contraceptive	322.7
15	47 / F	Encephalopathy	SSS	1	Oral Contraceptive	259.3
16	37 / M	Isolated Intracranial HPT	SSS, Bilateral TS, Bilateral SS	5	-	180.4
17	40 / F	Encephalopathy	SSS	1	Oral Contraceptive	78.9
18	38 / F	Focal Syndrome	SSS, Bilateral TS, Left SS, Left IJV	5	HIV	294.5
19	55 / F	Isolated Intracranial HPT	SSS	1	Meningitis	136.5
20	25 / M	Isolated Intracranial HPT	SSS	1	-	90.1
21	19 / M	Isolated Intracranial HPT	Left SS	1	Hyperhomocysteinaemia Neurosurgery procedure	159.7
22	54 / F	Focal Syndrome	Left TS, Left SS	2	HIV	322.7
23	24 / M	Cavernous Sinus Syndrome	Bilateral CS	2	Local head / face infection	289.2
24	51 / M	Encephalopathy	Left TS, Left SS, Left IJV	3	-	118.4
25	70 / F	Encephalopathy	Left TS, Left SS	2	-	136.5
26	57 / F	Focal syndrome	SSS	1	Meningitis	126.6

M = Male; F = Female; HPT = Hypertension; SSS = Superior Sagittal Sinus; TS = Transverse Sinus; SS = Sigmoid Sinus; CS = Cavernous sinus; IJV = Internal Jugular Vein

There was single sinus involvement in 38.5% (10/26) and multiple sinus involvement in 61.5% (16/26) of patients with CVT.

An elevated factor VIII level (>150IU/dL) occurred in 61.5% (16/26), followed by oral contraceptive use in 23.1% (6/26), pregnancy in 11.5% (3/26), meningitis in 11.5% (3/26), and HIV in 11.5% (3/26). There were no reported COVID-19 infections or vaccines received within the three months prior to the thrombotic event in any of the patients with CVT (Figure 1). In terms of a number of risk factors, with the inclusion of an elevated factor VIII level as a recognized risk factor, 50% (13/26) had multiple risk factors, 38.5% (10/26) had a single risk factor, and 11.5% (3/26) had no risk factors identified. The median time between the date of the CVT event and blood sampling was 8.17 months (range 3 to 76 months). At the time of blood sampling, 46.2% (12/26) were currently using oral anticoagulation.

FACTOR VIII LEVELS AND CONTROLS

The age-, sex- and HIV status-matched control group consisted of 52 participants (38 female; 14 male); the mean age was 41 years and age range was 19 to 75 years. The characteristics of the patients with CVT and controls are shown in Table 2. The mean factor VIII level was significantly higher for the patients with CVT as compared to controls (200.1 vs 156.9, p = 0.017) (Figure 2). Using the cut-off value of 150 IU/dL as per published literature, 61.5% (16/26) of patients with CVT had elevated factor VIII levels, compared to 50.0% (26/52) of controls (p = 0.335), with an odds ratio of 1.6 (95% CI 0.613–4.175). The age- and sex-adjusted odds ratio was 1.67 (95% CI 0.605–4.609). Using a higher cut-off value of 200 IU/dL, 42.3% (11/26) of patients with CVT had elevated factor VIII levels, compared to 15.4% (8/52) of controls (p = 0.009), with an odds ratio of 4.033 (95% CI 1.366–11.912); the age- and sex-adjusted odds ratio was 4.437 (95% CI 1.435–13.723).

Figure 3 shows the mean factor VIII level per number of cerebral venous sinuses involved in the patients with CVT. The mean factor VIII level was higher for the 16 patients with multiple (two or more) sinus involvement than for the

Table 2: Characteristics of patients with CVT and controls

	CVT patients n = 26	**Controls n = 52**
Mean age, years (SD)	40.30 (14.89)	41.40 (14.80)
Females, n (%)	19 (73.1)	38 (73.1)
Males, n (%)	7 (26.9)	14 (26.9)
Black, n (%)	18 (69.2)	34 (65.4)
Asian/Indian, n (%)	2 (7.7)	2 (3.8)
Mixed ethnicity, n (%)	1 (3.8)	3 (5.8)
White, n (%)	5 (19.2)	13 (25.0)
HIV-positive, n (%)	3 (11.5)	6 (11.5)
Episode of previous thrombosis, n (%)	0 (0.0)	0 (0.0)
Family history of thrombosis, n (%)	2 (7.7)	1 (1.9)
Mean factor VIII level, IU/dL (SD)	200.1 (91.18)	156.9 (56.65)
Elevated factor VIII level >150 IU/dL, n (%)	16 (61.5)	26 (50.0)
Elevated factor VIII level >200 IU/dL, n (%)	11 (42.3)	8 (15.4)

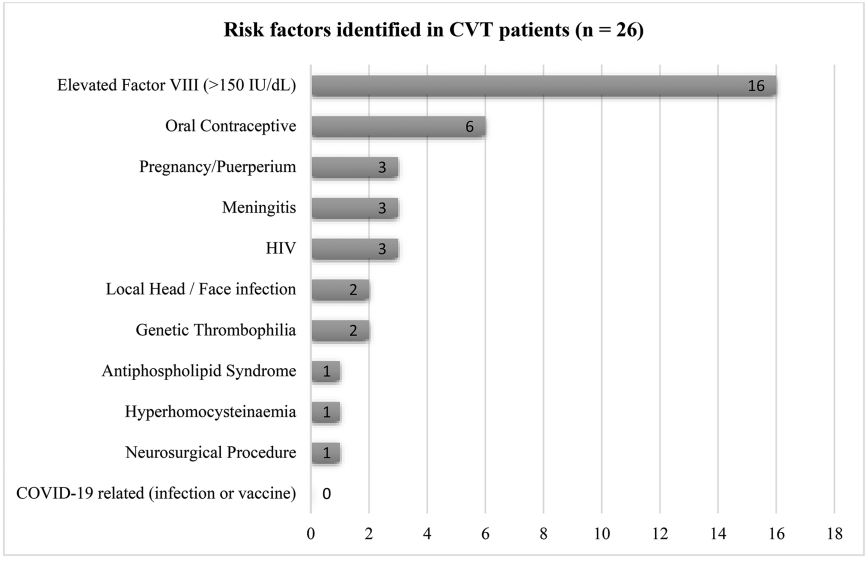

Figure 1: Risk factors identified in CVT patients

10 patients with single sinus involvement, but this was not statistically significant (218.4 vs 170.9; p = 0.201).

The mean factor VIII level was higher for the 12 patients with CVT using oral anticoagulation at the time of blood sampling than for the 14 CVT patients not using oral anticoagulation, but this was not statistically significant (225.5 vs 178.4, p = 0.105).

DISCUSSION

The Leiden Thrombophilia Study (LETS) from 1997 was the first study to report an association between an elevated factor VIII level and VTE.(5) However, an elevated factor VIII level in patients with CVT specifically has been under-reported and under-studied. We found that an elevated factor VIII level above 150 IU/dL was the most common (61.5%) risk factor in our study patients with CVT. Also, the mean factor VIII level was significantly higher for patients with CVT as compared to controls. Furthermore, an elevated factor VIII level above 200 IU/dL increased the risk of CVT approximately four-fold. This is in keeping with previous studies.(14–17)

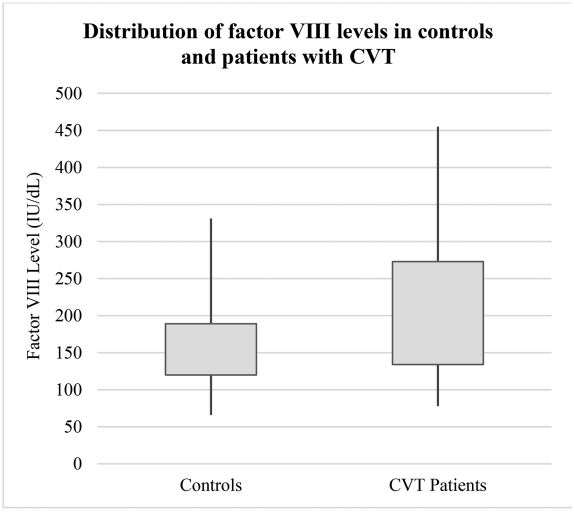

Figure 2: Data depicted as a box-and-whisker plot, with boxes indicating the 25th and 75th percentiles, and whiskers indicating the minimum and maximum values

Cakmak et al found an elevated plasma factor VIII level in 50% of patients with CVT, which was the most common prothrombotic risk factor in the study.(19) However, this study did not include a control group. In a case-control study from France in 2006, Bugnicourt et al demonstrated an elevated factor VIII level (>190 IU/dL cut-off value, the 95th percentile of the control group) in 25% of patients with CVT compared to 1.6% of controls.(14) With previously used cut-off values, an elevated factor VIII level (>150 IU/dL) was found in 62.5% of patients with CVT and was the most common prothrombotic risk factor identified.(14) In an Iranian case-control study in 2011, Shahsavarzadeh et al. concluded that an elevated factor VIII level (>179 IU/dL cut-off value, the 95% percentile of the control group) was associated with a ten-fold increased risk of CVT.(15) In a case-control study from India in 2014, Anadure et al. demonstrated an elevated factor VIII level (>170 IU/dL cut-off value, the 90th percentile of the control group) in 73% of patients with CVT compared to 8% of controls, and concluded that an elevated factor VIII level was associated with an 18-fold increased risk of CVT.(16) In a larger case-control study based in Amsterdam in 2018, Vecht et al. demonstrated an elevated factor VIII level (>150 IU/dL) in 83.6% of patients with CVT and concluded that an elevated factor VIII level was associated with a 15-fold increased risk of CVT.(17) These studies have all concluded that an elevated plasma factor VIII level is a common and strong risk factor for CVT. Hence, including a plasma factor VIII level in the aetiological work-up of patients with CVT should definitely be considered.

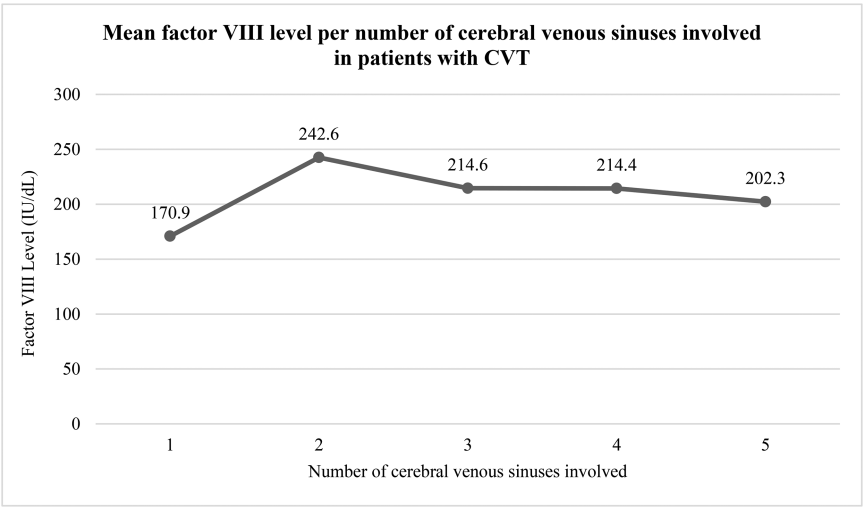

Figure 3: Association of the mean factor VIII level and number of cerebral venous sinuses involved in patients with CVT

However, these four controlled studies were underpowered to determine whether an elevated factor VIII level is also associated with an increased risk of recurrent CVT or an increased risk of another type of thrombosis after CVT. In our study, none of the patients with CVT had any previous episodes of thrombosis. We followed up our patients with CVT for up to 76 months and did not find any recurrence and will continue to evaluate our patients on a yearly basis.

The influence of the acute phase response on the factor VIII level in patients with venous thrombosis was previously a matter of debate since factor VIII levels are known to rise in response to the acute phase reaction. However, longitudinal follow-up studies have clearly shown that an elevated plasma factor VIII level identified in patients with VTE tends to remain persistently elevated for many years (in some studies, in excess of five years).(6,20,21) Plasma factor VIII levels have not shown any correlation with fibrinogen, C-reactive protein, or erythrocyte sedimentation rate.(20) Therefore, it is implied that in the vast majority of patients with an elevated factor VIII level, the post-thrombotic acute phase response is of inconsequential importance. Nevertheless, in order to avoid this debatable acute phase response impact on the factor VIII level, most studies perform the factor VIII level measurement at least three months after the thrombotic event, which we have adhered to in our study.(4)

The mean factor VIII level for patients with CVT with single sinus involvement was below 200 IU/dL, as compared to the mean factor VIII levels above 200 IU/L for patients with two, three, four, and five sinuses involved. However, the mean factor VIII levels in patients with single sinus involvement compared to patients with multiple sinus involvement, was not statistically significant. This association has not been reported before and needs confirmation in larger studies.

The clinical presentation and radiological features in our patient group with CVT are in line with previous international studies. Based on Bousser et al, the four main clinical patterns of presentation accounted for all our patients with CVT; isolated intracranial hypertension in 34.6%, encephalopathy in 30.6%, focal syndrome in 26.9%, and cavernous sinus syndrome in 7.7%.(22) According to previous studies, the most frequently involved cerebral venous sinuses are the superior sagittal sinus, transverse sinus, and sigmoid sinus.(23,24) We found that these sinuses were also the three most frequently involved cerebral venous sinuses in our patients with CVT.

There were several limitations in our study. Firstly, we did not determine the ABO blood group or vWF level in the CVT patients or controls, which may have influenced the factor VIII level. Secondly, outpatient-based controls (without a history of previous thrombosis) were used, which may not have been accurately representative of the community-based population. Thirdly, the sample size of both groups was relatively small, and finally, limitations associated with retrospective studies apply to our study as well.

CONCLUSION

This is the first study from Southern Africa that demonstrates that an elevated factor VIII level is a common risk factor in patients with CVT. We also found that an elevated factor VIII level above 200 IU/dL was associated with a fourfold increased risk of CVT and was likely to involve more than one cerebral venous sinus. Therefore, we recommend that testing for factor VIII levels should be included in the aetiological work-up of CVT.

DECLARATIONS

Conflicting interests: The Authors declare that there is no conflict of interest.

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