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Original Article

Prothrombin G 20210 A mutation in Patients with Cerebral Venous Sinus Thrombosis at Sohag university hospital

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Abstract

Background: Cerebral venous sinus thrombosis (CVST) is a rare thrombotic disease with its estimated annual incidence of 3–4 cases per million. Patients with genetic thrombophilia such as prothrombin G20210A mutation display a higher propensity to CVST when compared to other venous thrombosis. The aim of the study was to assess the significance of prothrombin G20210A mutation as a risk factor for patients with CVST.

Objective: This study aimed to assess the significance of prothrombin G20210A mutation as a risk factor for patients with CVST at Sohag University Hospital.

Methods: This case control study was carried out on 56 participants. They were divided into two equally groups; case group [diagnosed with CVST], control group [healthy participants]. Participants were subjected to the following: genetic and acquired risk factors for thrombosis including prothrombin gene (G20210 A) mutation, whereas patients' group were subjected to history of previous thrombosis, duration of illness, presenting symptoms, oral contraceptives or HRT usage, vasculitis, hematological disorders, presence of papilledema and cranial nerve palsy, Glasgow Coma Scale (GCS), Modified Rankin Score (mRs) at discharge.

Results: In the current study, 14.29 % of CVST patients were heterozygous for the prothrombin G20210A mutation while only one person (3.57%) in the control group showed this mutation. CoCS/HRT and protein S deficiency were significantly higher in cases than controls **.** mRs at admission was insignificantly related to prothrombin gene mutation (p=0.134). mRs at discharge of patients with gene mutation group and the group of patients without mutation was not statistically significant. Regarding radiological findings of positive and negative groups there were insignificant difference between them.

Conclusions: Our study revealed that although the prevalence rate of PTH gene mutation in our CVST patients was higher than reported in previous studies it is still statistically insignificant risk factor for CVST,

Keywords: Prothrombin, Gene Mutation G20210, Cerebral Venous Sinus Thrombosis.

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Introduction:

The estimated yearly incidence of cerebral venous sinus thrombosis (CVST), a rare thrombotic disorder, is 3–4 occurrences per million .[1]

Recent research, however, indicated a signify-cantly higher prevalence of 13.2-15.7 incidents per million.[2]

Diagnostic errors and delays are not uncommon. [3, 4]

Blood clotting in the dural venous sinuses, cortical veins, and the proximal segment of the jugular veins are symptoms of cerebral venous sinus thrombosis (CVST) .[5]

Every age group may be impacted. However, due to pregnancy, puberty, and the use of oral contraceptives (OCPs), there is a slight prevalence among young women. (6)

There are many risk factors that have been linked to CVST, which makes determining the cause extremely difficult. As an illustration, a research from Italy found a significant link between CVST and oral contraceptive use.(7)

Additionally, compared to other venous thrombosis, patients with genetic thrombophilia, such as the prothrombin G20210A mutation, have a higher predisposition to CVST .(8)

The symptoms can include a headache, convulsions, focal neurological indications, impaired mental status, or any combination of these. The frequency of CVT is modest among people who experience these neurologic symptoms. (9, 10)

Visualizing clots directly or indirectly in the brain's venous circulation is a key component of CVT diagnosis. The imaging techniques that are employed in clinical practice include non-contrast CT (NCCT), non-contrast CT with CTV, routine MRI without vascular imaging (R-MRI), or structural MRI with specialized contrast-enhanced magnetic resonance venography .(11, 12) Patients with CVST may recover fully or experience neurological impairments that last a lifetime. (13)

Methodology:

Study Design and patients:

A total of 56 people were involved in this case control research. They were split evenly into two groups: the case group (participants with a diagnosis of CVST), and the control group (participants in good health). Between October 2019 and October 2020, they were admitted into the Sohag university hospital's neurology unit , Sohag governorate , Egypt. CVST was identified as a consequence of a neurologist's assessment of the clinical signs and symptoms as well as the MRI and MRV scan results.

The Sohag Faculty of Medicine's Scientific and Ethical Committees gave this study their blessing.

All of the subjects gave their informed consent.

Patients having ischemic strokes, lesions that occupied space, subdural hematoma, subarachnoid hemorrhage, or fungal infections of the rhino- or oto-cerebral regions were disqualified.

A total of 28 people made up the healthy control group, who were all of the same age, sex, and geographic origin as the CVT group with a 22–42 year age range and a mean age of 28±71. All demographic information, inherited and acquired thrombosis risk factors, including the prothrombin gene G20210 A mutation were noted. Three men and 25 women who were referred to our Institute between October 2019 and October 2020 for a first episode of CVT made up the case group of 28 consecutive, unrelated individuals that we investigated. MR venography and brain MRIs were used to diagnose CVT. Subcutaneous low molecular weight heparin was frequently used as the first line of treatment, followed by oral anticoagulants, symptomatic medications (anticonvulsants, analgesics), and lowering of elevated intracranial pressure. Both the demographic data and the medical information were documented. The length of the sickness and the symptoms that presented themselves, including headache, nausea, seizures, focus deficit, visual impairment, diplopia, and altered sensorium were noted. The use of oral contraceptives or HRT, vasculitis, and hematological diseases were identified, as well as a history of prior thrombosis. The presence of cranial nerve palsy and papilledema was noted. The National Institutes of Health Stroke Scale (NIHSS) and the Global Coma Scale (GCS) were used to evaluate consciousness at admission. Modified Rankin score (mRs) was used to evaluate the prognosis at discharge. All patients had a hemogram, liver and kidney function tests, and serum electrolytes done as basic investigations.

The patients' inherited and acquired CVST risk factors were evaluated: Antithrombin III, protein C, and protein S deficiency; presence of lupus anticoagulant; prothrombin gene G20210A mutation.

Finding a mutation in the prothrombin gene (FII G20210A): G to by using the PCR-RFLP approach, a substitution at nucleotide 20210, which is located in exon 14 of factor II, was also investigated. Using the forward primer 5'TCTAGAAACAGTTGCCTGGC3' and the reverse primer 5'ATAGCACTGGGAGCATTGAAGC3',a region of 345 bp of exon 14 was amplified. For factor V, PCRs were conducted under the same circumstances. While 20210G remained undigested (345 bp) following digestion with Hind III, 20210

Aallele was digested into two pieces of 322 and 23 bp.[14]

Statistic Analysis

IBM, Chicago, Illinois, USA's SPSS v25 was used for the statistical study. Histograms and the Shapiro-Wilks test were employed to assess the normality of the data distribution. Unpaired student t-test was used to evaluate quantitative parametric data that were reported as mean and standard deviation (SD). The Mann Whitney-test was used to analyze quantitative non-parametric data that were given as median and range. When necessary, qualitative data were compared using the chi-square (X2) or Fisher's Exact test and reported as a number and a percentage. Statistical significance was defined as a two tailed P value 0.05.

Results:

There was no statistically significant difference in any of the demographic factors between CVST cases and healthy controls. In the current investigation, only one person (3.57%) in the control group had the prothrombin G20210A mutation, which had a non-statistically significant p value (p=0.352), but 14.29% of CVST patients had it. Protein S deficiency and CoCS/HRT levels were considerably greater in patients compared to controls. accordingly (P = 0.005 and 0.023). The other risk factors, however, did not differ significantly between the case group and the control group. (Table 1)

Table 1: Demographic data and risk factors of cases and controls

		Cases (n = 28)	Controls (n = 28)	P value
Age (years)		29.82 ± 7.30	28.71 ± 5.09	0.513
Gender	Male	3 (10.71%)	3 (10.71%)	1
	Female	25 (89.29%)	25 (89.29%)	
Residence	Rural	17 (60.71%)	15 (53.57%)	0.589
	Urban	11 (39.29%)	13 (46.43%)	
Occupation	Housewife	22 (78.57%)	20 (71.43%)	0.759
	Employee	3 (10.71%)	4 (14.29%)	1
	Student	3 (10.71%)	4 (14.29%)	1
CoCS/HRT		16 (57.14%)	5 (17.86%)	**0.005***
Postpartum		4 (14.29%)	0 (0%)	0.112
Pregnancy		1 (3.57%)	2 (7.14%)	1
Postoperative		4 (14.29%)	0 (0%)	0.112
Anti-thrombin 3 deficiency		5 (17.86%)	1 (3.57%)	0.193
Protein S deficiency		6 (21.43%)	0 (0%)	**0.023***
Protein C deficiency		1 (3.57%)	1 (3.57%)	1
Prothrombin G20210A mutation		4 (14.29%)	1 (3.57%)	0.352
Anemia		5 (17.86%)	2 (7.14%)	0.422
Vasculitis		3 (10.71%)	0 (0%)	0.236
History of Previous thrombosis		2 (7.14%)	0 (0%)	0.491

Data represented as mean ± SD or frequency and percent (%).

NIHSS ranged between 0 and 22 with a median value of 3.50. GCS ranged between 9 and 15 with a mean value of 13.43 ± 2.06. There were 25 (89.29%) patients had a headache, 11 (39.29%) patients had seizures, 13 (46.43%) patients had focal neurological deficit, 13 (46.43%) patients had altered consciousness and 6 (21.43%) patients had papilledema. (Table 2)

Table 2: Clinical features of CVST patients at admission and radiological findings in CVST patients presented in table 2

		Cases (n = 28)
NIHSS at admission		3.50 (0-22)
GCS (admission)		13.43 ± 2.06
Headache		25 (89.29%)
Seizures		11 (39.29%)
Focal neurological deficit		13 (46.43%)
Altered consciousness		13 (46.43%)
Papilledema		6 (21.43%)
Radiological findings		
Superior sagittal sinus		16 (57.14%)
Inferior sagittal sinus		3 (10.71%)
Straight sinus		4 (14.29%)
Transvers sinus		18 (64.29%)
Sigmoid sinus		14 (50.00%)
Number of sinuses	Single	11 (39.29%)
	Multiple	17 (60.71%)
Cortical veins		17 (60.71%)
Internal jugular vein		2 (7.14%)
Non hemorrhagic (Ischemic) parenchymal lesion		17 (60.71%)
Hemorrhagic parenchymal lesion		9 (32.14%)

Data presented as Mean ± SD, Median, frequency (percent).

All clinical features of the CVST were insignificantly different between single sinus thrombosis and multiple sinus affection. (Table 3)

Table 3: Association between number of thrombosed sinuses and clinical features of the CVST patients

	Single (n = 11)	Multiple (n = 17)	P value
NIHS at admission	3	5	0.141
GCS (admission)	14.09 ± 1.38	13.00 ± 2.35	0.176
Headache	11 (100%)	14 (82.35%)	0.499
Seizures	4 (36.36%)	7 (41.18%)	1
Focal neurological deficit	4 (36.36%)	9 (52.94%)	0.460
Altered consciousness	5 (45.45%)	8 (47.06%)	1
Papilledema	1 (9.09%)	5 (29.41%)	0.355

Data presented as Mean ± SD, Median, frequency (percent

mRs was significantly lower at discharge compared to admission (P <0.001). (Table 4)

Table 4: Comparison between mRs of CVST patients at admission and discharge

	Admission (n = 28)	Discharge (n = 28)	P value
mRs	2.00	1.00	**<0.001***

Data presented as median

All the Demographic data were insignificantly different between patients with PTH gene mutation and those without gene mutation. (Table 5)

Table 5: Association between demographic variables and PTH gene mutation

		+ve (n = 4)	-ve (n = 24)	P value
Age (years)		31.00 ± 5.48	29.63 ± 7.64	0.731
		25 – 37	16 – 43	
Gender	**Male**	1 (25%)	2 (9.80%)	0.445
	Female	3 (75%)	22 (8.33%)	
Residence	**Rural**	2 (50%)	15 (62.50%)	0.642
	Urban	2 (50%)	9 (37.50%)	
Occupation	**Housewife**	3 (75%)	13 (54.17%)	0.624
	Employee	0 (0%)	10 (41.67%)	0.264
	Student	1 (25%)	0 (0%)	0.143

As regard clinical presentations of CVST patients there was no significant difference between patients with PTH gene mutation and those without gene mutation, except papilledema which was significantly higher in patients with PTH gene mutation than those without gene mutation (P =0.022). (Table 6)

Table 6: Association between PTH gene mutation and both risk factors and clinical presentation of CVST patients.

	+ve (n = 4)	-ve (n = 24)	P value
mRs at admission	1.5	1	0.134
mRs at discharge	2.4	1.2	0.217
NIHS at admission	2.00	4.50	0.174
GCS (admission)	15.00 ± 0	13.17 ± 2.12	0.101
Headache	4 (100%)	21 (41.18%)	1
Seizures	1 (25%)	10 (41.67%)	1
Focal neurological deficit	2 (50%)	11 (45.83%)	1
Altered consciousness	0 (0%)	13 (54.17%)	0.102
Papilledema	3 (60%)	3 (12.50%)	**0.022***

Data presented as Mean ± SD, Median, frequency (percent)

Regarding radiological findings of positive and negative groups there were insignificant difference

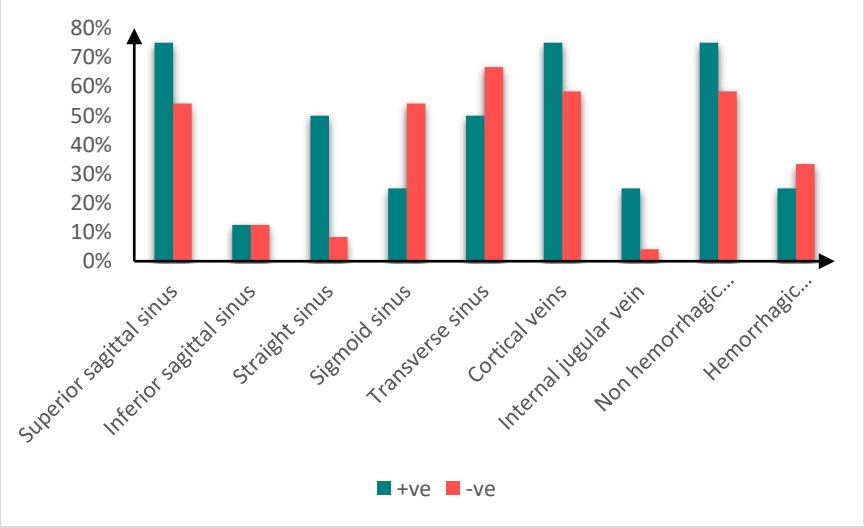

Figure 1: Radiological findings of CVST patients with PTH gene mutation and those without gene mutation

Discussion

In all stroke syndromes, cerebral venous sinus thrombosis (CVST) accounts for about 0.5%. The many CVST presentations can make diagnosis challenging. Additionally, the condition may be harmful because a significant number of individuals have increased intracranial pressure (ICP), localized infarcts, and intracerebral hemorrhage. [15]

Our research supported the findings of Boncoraglio et al. [16] who found no association between the prothrombin gene mutation G20210 A and CVST (P > 0.05). There was no statistically significant difference between the prothrombin G20210A mutant patients and the control group, according to Altinisik et al. [17] (P >.01). Our findings supported those of Ashjazadeh et al. [14], who likewise came to the conclusion that the prevalence of the prothrombin II (G20210A) mutation in CVST patients was not statistically significant (p=1).

In line with our present research, a study with 16 Lebanese individuals with CVST, Otrock et al. [18] observed that the factor II G20210A mutation was not a risk factor for CVST.

Our findings are at odds with those of Lichy et al. [19] and numerous other investigations, which found a statistically significant association between the prothrombin G20210 A mutation and CVST .[20]Additionally, Martinelli et al. [21] found that women who take OCP who have the prothrombin II (G20210A) gene mutation have an increased chance of developing CVST. In line with Reuner et al. [22], Bombeli et al. [22], and Rodrigues et al. [23], we also discovered that patients with CVST tended to use oral contraception more frequently (57.14%) than healthy controls (17.86%). This difference was statistically significant (p = 0.023). Martinelli et al.'s. [21] study indicated that oral contraceptives are highly linked to CVST, raising the risk by a factor of about 20. This finding is similar to that of our study. Pan et al. [24] observed that the proportion of oral contraceptive use and HRT in Chinese female patients with CVST (18.3%) was lower than what was seen in our study.

Vasculitis was discovered in 10.71% of the individuals in our investigation, and Yilgor et al. [25] observed a similar result. However, the prospective multinational observational research ISCVT, which included patients with symptomatic CVT who were over 15 years old, indicated that only 3% of CVST had vasculitis.[26]

According to Boncoraglio et al. [16] and Pan et al. Pan, the transverse sinus was the sinus most frequently implicated, followed by the sagittal sinus. This finding is consistent with our findings. On the other hand, according to Kalita et al. [27], 42.2% of CVST had sigmoid sinus thrombosis, which was followed by equal thrombosis of the superior sagittal and transverse sinuses in 62.5% of cases.

Except for papilledema, which was more common in patients with the mutation than in patients without the mutation (P = 0.022), we did not find any statistically significant differences between clinical features, radiological findings, or outcome in patients with prothrombin gene G20210A mutation compared to those without the mutation.

According to a different study by Kalita et al. [27], the weight of risk factors had no bearing on the clinical severity, MRI results, degree of MRV abnormalities, or outcome. Contrarily, Ventura et al.[28] discovered that recently identified thrombophilic factors, such as the prothrombin G20210A mutation, appear to be important in the etiology of CVT in patients who have already been diagnosed with the condition, with the potential for an atypical and severe clinical presentation.

In contrast to Coutinho et al. [29] who reported a strong association between anemia and CVST (patients vs. controls, 27% vs. 6.5%), our study demonstrated that anemia was more common in cases than control group but that difference was not statistically significant. This could be explained by the fact that most of our cases were females, and a lower risk of CVT among women with anemia might be related to the high prevalence of female patients. Oral contraceptives are a well-known CVT risk factor, however some research has found that these medications also lessen the risk of anemia, which may lead to a lower prevalence of anemia among women with CVT. No statistically significant association was discovered in our investigation.

Our results are in direct opposition to those of Roosendaal et al.[30], who found that in familial instances, carriers of protein C deficiency had a higher risk of thrombosis than relatives without a deficit.

But our research has significant drawbacks. Small sample size is first. Second, it is difficult to draw generalizations from the study sample because most of the participants lived in the Sohag Governorate and all data were gathered at Sohag University Hospital. Thirdly, we did not assess other inherited risk factors such as FV G1691A(Leiden), FV H1299R (R2), MTHFR C667T, B-Fibrinogen -455 GA, PAI-1 4G/5G, and APO E genotype mutations which may overlap with PTH gene mutation in patients with CVST.

Conclusions

Despite the fact that the prothrombin gene G20210A mutation was not determined to be a significant risk factor for CVST in the current investigation, the prevalence rate of PTH gene mutation in our CVST patients was higher than that discovered in earlier studies carried out in Africa and Asia. Our findings also showed a strong association between CVST and the use of oral contraceptives or hormone replacement treatment.

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Ethics

Ethical approval for this study was obtained from the ethics committee of the University of Sohag**.**

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.B.,G.F., E.H.,designed the study. M.A. and M.K. gathered data. All authors contributed to the interpretation of the data. All authors edited the manuscriptand approved the final version of the manuscript**.**

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