

## Cerebral Venous Thrombosis: Risk Factors, Possible Etiologies and Outcome

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### Abstract

**Background:** CVT represented 1% of all strokes. The most frequent risk factors associated conditions for CVT are genetic prothrombotic conditions, antiphospholipid syndrome and other acquired prothrombotic diseases, including cancer, oral contraceptives, puerperium and pregnancy, infections and trauma.

**Aim of the Work:** Is to study possible etiologies, risk factors, clinical presentations, radiological features and outcome of cerebral venous thrombosis during child bearing period.

**Patients and Methods:** This study was conducted in the Neuropsychiatric Department Tanta University Hospital on 82 patients with CVT, aged from 15–45 years. They were classified into female and male groups plus 20 control group matched with age. All patients were subjected to full history taking, neurologic examination including evaluation by Glasgow coma scale (GCS) and National Institute of Health Stroke Scale (NIHSS), laboratory investigations, neuroimaging including: CT, MRI, MRV were done and follow-up by Modified Rankin Scale (MRS) after 3 months.

**Results:** OCP was the most common risk factor followed by postpartum state. Single risk factor was presented in 48.8% and multiple risk factors were presented in 22%. Headache was the most common presenting symptoms followed by GTCS and motor deficit. Headache, GTCS, motor deficit and encephalopathy were more in females while papilledema, focal seizures, sensory deficit and aphasia were more in males. Hypercoagulable state was the most common etiology followed by antiphospholipid syndrome and SLE. Hypercoagulable state was most common in both sex, while sepsis and Behcet were significantly more common in males. Superior sagittal sinus (SSS) was the most common affected sinus followed by transverse and sigmoid sinuses. Single affected sinus was in 65.9%, while multiple affected sinuses was in 31.7% of patients. 12 patients (14.6%) were died. The most common cause of death was herniation followed by uncontrolled seizures. Factors associated with poor outcome were GCS less than 10 and NIHSS more than 14.

**Conclusion:** Headache is the most common presenting symptoms followed by motor deficit. D-dimer is positive in

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76%. Hypercoagulable state is the most common etiology followed by antiphospholipid syndrome and SLE. SSS is the most common affected sinus then transverse sinus and sigmoid one. Female sex, GCS less than 10, NIHSS more than 14 and patients presented by headache have poor outcome.

**Key Words:** CVT– Etiology – Risk factors– Outcome.

### Introduction

**CEREBRAL** venous thrombosis (CVT) is a stroke type that is caused by thrombus in  $\geq 1$  of the venous sinuses and manifests primarily as headache. CVT makes up 0.5% to 1% of all strokes, but is the stroke type that shows the most prominent differential sex prevalence. In adulthood, the majority of affected individuals are women [1].

CVT is caused by systemic or local imbalances in pro-thrombotic and thrombolytic processes. As venous blood is forced back into small vessels and capillaries, an increase in venous and capillary pressure occurs, disruption of the blood brain barrier and decrease in cerebral perfusion pressure develops, which leads to cerebral oedema, local ischaemia and often intracerebral haemorrhage [2].

Pregnancy and the puerperium period are times of increased risk for venous thrombosis for women, including CVT. The greatest risk periods for CVT include the third trimester and the first 4 postpartum weeks. Cesarean delivery appears to be associated with a higher risk of CVT after adjustment for age, vascular risk factors, presence of infections, hospital type, and location [3].

The clinical presentation of cerebral venous thrombosis can be highly variable. Onset of symptoms and signs may be acute, subacute or chronic. Four major syndromes have been described: Isolated intracranial hypertension, Focal neurological abnormalities, Seizures and Encephalopathy [4].

Diagnostic modalities currently used for the confirmation of CVT include computed tomography (CT), magnetic resonance imaging (MRI), and cerebral angiography. Current recommendations incorporate venographic imaging in any case with clinically suspected CVT even with initially negative CT or MRI [5].

Cerebral venous thrombosis usually has a good prognosis, but can result in death or permanent disability. The main cause of death with acute CVT is transtentorial herniation secondary to a large hemorrhagic lesion. Status epilepticus, medical complications, and pulmonary embolism are among the other causes of early death [6].

*Aim of the work:* Is to study possible etiologies, risk factors, clinical presentations, radiological features and outcome of cerebral venous thrombosis during child bearing period.

### Patients and Methods

This study was conducted in the Neuropsychiatry Department of Tanta University Hospital on 82 patients of cerebral venous thrombosis (CVT) in the period between December 2015 and December 2016. They were classified into female group (66 patients) and male group (16 patients). Possible risk factors and etiologies of CVT were assessed through either imaging or laboratory studies. Our patients were subjected to follow-up after three months of admission date including evaluation of their clinical and functional outcome using Modified Rankin Disability Scale.

Each patient was subjected to full history taking, thorough neurological examination including GCS and NIHSS, brain CT, MRI and MRV. CT brain was done to 74 patients excluding pregnant patients and MRI brain and MRV were done to 82 patients. Routine laboratory investigations including ESR, CRP, liver functions, renal functions, blood picture and Triglycerides. Specific laboratory investigations including D-dimer, ANA, anti-double strand DNA, anticardiolipin antibodies, lupus anticoagulant, antiphospholipid antibodies and thrombophilia testing.

### Results

The mean age of males was higher than females, but without significant difference. 75% of males were from rural area versus 60.6% for females. The mean hospital stay of females was higher than males, but without significant difference (Table 1).

Table (1): Demographic data of female versus male.

	Female (n=66)	Male (n=16)	Test of sig.	p- value
Age: (mean $\pm$ SD)	30.272 $\pm$ 7.74	32.62 $\pm$ 8.89	t=0.85	0.39
Residency (n, %):			$\chi^2=0.10$	0.28
Rural	40 (60.6)	12 (75.0)		
Urban	26 (39.4)	6 (25.0)		
Hospital stay (mean $\pm$ SD)	6.81 $\pm$ 3.06	6.25 $\pm$ 2.04	U=0.30	0.75

Oral contraceptive pills was the most common risk factor (42.4%) followed by postpartum state (33.3%), pregnancy (12.2%), abortion (12.1%), smoking (7.3) and addiction, DM, HTN (4.9%) and past history of DVT (2.4%). The risk factors of significance were OCP and postpartum state. 48% of patients had one risk factor, 22% had multiple risk factors and 29.3% did not have any risk factor (Table 2).

Table (2): Possible risk factors among CVT patients.

	CVT (n=82)		Test of sig.	p- value
	No.	%		
<i>Gender specific risk factors (N= 66):</i>				
Pregnancy	8	12.1	FE=0.99	0.31
OCP	28	42.4	$\chi^2=10.30$	0.001*
Postpartum state	22	33.3	FE=5.69	0.01*
Abortion	8	12.1	FE=0.99	0.31
Addiction	4	4.9	FE=0.13	0.71
Smoking	6	7.3	FE=0.01	0.92
<i>Comorbidity:</i>				
No	72	87.8		
HTN	4	4.9		
DM	4	4.9		
DVT	2	2.4		

Headache, GTCS, motor deficit and encephalopathy were more common in females while papilledema, focal seizures, sensory deficit and aphasia were more in males, but only GTCS showed significant difference more in females versus males (45.5%, 0%) and focal seizures showed significant difference more in males versus females (12.5%, 0%) (Table 3).

Behcet was present in 12.5% in males and 0.0% in females and the difference was statistically significant (p-value 0.04). Sepsis was present in 25% of males and 0% of females and the difference was statistically significant (Fig. 1).

Cord sign was presented in 18.2% of females and 37.5% of males in CT and in 21.2% and 12.5% in MRI. Empty delta sign was presented in 33.3% of females and 37.5% of males. Parenchymal lesions were presented in 9.1% in females in CT and 51.5% in MRI. All neuroradiology parameter showed non-

significant difference except for normal MRI ( $p=0.007$ ) which was significant more in males. (Table 4).

The most common sinus affected was SSS (65.9%) followed by transverse sinus (43.9%) and sigmoid sinus (17%). The least affected sinus was dural sinus (4.9%). single sinus affected was in 65.9% and multiple affected sinuses were in 31.7% of patients (Fig. 2).

85% of patients were survived. 94.1% showed complete improvement, while 14.6% were dead. 87.9% of females and 75% of males were survived .89.7% of females and 12% of males showed complete recovery. 8 females (12.1%) and 4 males (25%) were died with no significance regarding morbidity and mortality in both sexes (Table 5).

There was statistically significant relationship between hypercoagulable state and mortality ( $p=0.004$ ) while sepsis, SLE, antiphospholipid syndrome and Behcet had non-significant relation with outcome (Table 6).

All risk factors showed no significant relationship with morbidity and mortality (Table 7).

Table (3): Clinical pictures of CVT female versus male patients.

	Females (n=66)		Males (n=16)		test	p-value
	No.	%	No.	%		
<b>Isolated ICT:</b>						
Headache	48	72.7	10	62.5	0.25	0.61
Papilledema	20	30.3	8	50.0	$\chi^2=2.22$	0.13
<b>Seizures:</b>						
GTC seizures	30	45.5	0	0.0	$\chi^2=11.46$	0.001 *
Focal seizures	0	0.0	2	12.5	4.02	0.04*
<b>Focal deficit:</b>						
Motor deficit	28	42.4	4	25.0	$\chi^2=1.64$	0.20
Sensory deficit	4	6.1	2	12.5	0.12	0.72
Aphasia	2	13.0	2	12.5	0.87	0.35
Encephalopathy	6	9.1	2	12.5	0.00	0.95

Table (4): Radiological features among CVT patients.

	Females (n=66)		Males (n=16)		Fisher's Exact test	p-value
	No.	%	No.	%		
<b>CT (n=74):</b>						
Normal	14	21.1	4	25.0	0.00	0.99
Edema	32	48.5	8	50.0	0.01	0.91
Cord sign	12	18.2	6	37.5	1.79	0.18
Parenchymal lesion	6	9.1	2	12.5	0.00	0.95
Not done						
<b>MRI (n=82):</b>						
Normal	10	15.2	8	50.0	7.21	0.007*
Cord sign	14	21.2	2	12.5	0.19	0.66
Empty delta sign	22	33.3	6	37.5	0.00	0.75
Parenchymal lesion	34	51.5	4	25.0	3.64	0.056
<b>MRV (n=82):</b>						
Normal	2	3.0	2	12.5	0.687	0.35
Abnormal	64	97.0	14	87.5		

Table (5): Outcome among CVT patients.

	Females (n=66)		Males (n=16)		Fisher's Exact test	p-value
	No.	%	No.	%		
<b>Morbidity:</b>						
Total improvement	52	89.7	12	100.	0.36	0.54
Survived with death	6	10.3	0	0.0	0.36	
<b>Mortality:</b>						
Died	8	12.1	4	25.0	0.43	0.51

Table (6): Relationship between possible etiology and outcome.

	Morbidity		p-value	Mortality	
	Total Improvement (n=64) No. (%)	Improved with deficit (n=6) No. (%)		Died (n=12) No. (%)	p-value
Hypercoagulable state	42 (56.3)	4 (66.7)	0.95	2 (16.7)	0.004
Local infection	2 (3.1)	0 (0.0)	0.39	2 (16.7)	0.18
Not detected	4 (6.3)	2 (33.3)	0.13	2 (16.7)	0.72
SLE	8 (12.5)	0 (0.0)	0.80	2 (16.7)	0.96
Antiphospholipid syndrome	6 (9.4)	0 (0.0)	0.98	4 (33.3)	0.052
Behcet	2 (3.1)	0 (0.0)	0.85	0 (0.0)	0.68
Malignancy	0 (0.0)	0 (0.0)	-	0 (0.0)	

Table (7): Relationship between possible etiology and outcome.

	Morbidity		p-value	Mortality	
	Total Improvement (n=64) No. (%)	Improved with deficit (n=6) No. (%)		Died (n=12) No. (%)	p-value
Pregnancy	6 (9.4)	2 (33.3)	0.13	0 (0.0)	0.59
OCP	24 (37.5)	2 (33.3)	1.00	2 (16.7)	0.20
Delivery	18 (28.1)	0 (0.0)	0.32	4 (33.3)	0.72
Addiction	4 (6.3)	0 (0.0)	1.00	0 (0.0)	1.00
Smoking	4 (6.3)	0 (0.0)	0.53	2 (16.7)	0.21
Abortion	6 (9.4)	1 (11.1)	1.00	2 (16.7)	0.48
<i>Comorbidity:</i>					
HTN	2 (3.1)	0 (0.0)	1.00	2 (16.7)	0.15
DM	4 (6.3)	0 (0.0)		0 (0.0)	
DVT	2 (3.1)	0 (0.0)		0 (0.0)	

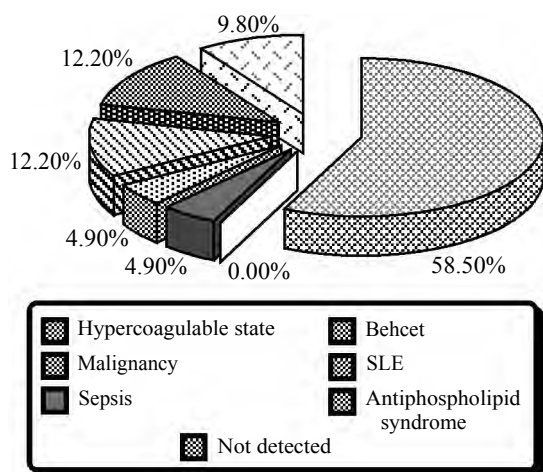


Fig. (1): Showing possible etiology among CVT patients.

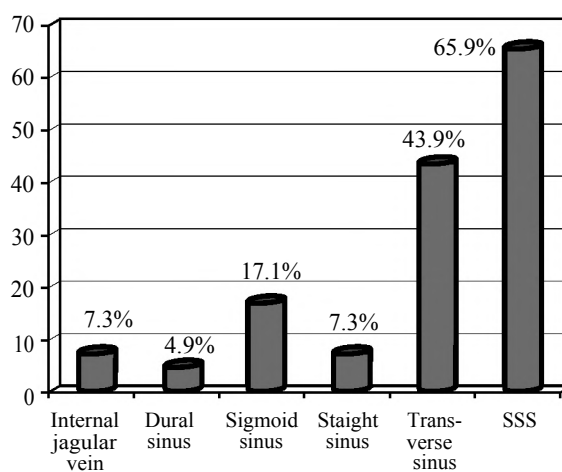


Fig. (2): Showing affected sinuses in CVT patients.

**Discussion**

In the present study, high predominance of female involvement was noticed (80%), that was in agreement with Souirti et al. and Irene et al. studies in which females were more affected than males, Also Zuurbier et al., stated that CVT was higher in females compared to males similar to the present study and they attributed that to the increased use of oral contraceptive pills, improved access to health care for women and increased frequency of CVT diagnosis in women [7-9].

The mean age of our study patients was 31 years old with females being more likely to present at a younger age compared to males and that was in accordance to Lim et al., study in which the mean age of females to males (33 versus 45 years), this could be attributed to the higher incidence of CVT among females during child bearing period [10].

Coutinhlo et al. stated that women had a better prognosis than men (complete recovery 81% versus 71%), while in our study 100% of men showed complete recovery versus 89.7% of women, which is mostly due to the lower spectrum of age in the current study (15-45) compared to the previous study, in which increase age of poor prognosis due to increased risk of malignancy and infections in older age [11].

In addition to the variation in clinical presentations, the etiology of CVT is commonly multifactorial, with a large portion of patients having more than one cause or predisposing factor. OCP was the most common gender specific risk factors 42.4%, that was in agreement with Terazzi et al., Ferro et al. and Dentali et al., [12-14].

Coutinhlo et al., postulated that hypercoagulable state was more or less similar in females and males (22% versus 25%). Infections were less common among males (10% versus 21%), while in our study, the incidence of hypercoagulable state was much

higher in females compared to males (63.6% versus 37.5%), because of the increase frequency of coagulopathy in pregnant, post-partum and females taking oral contraceptive pills. and infection was in 25% of men, but not detected in women in the present study [11].

In the present study there was non-significant relationship between gender specific risk factors and outcome, while in Patil et al., and Duman et al., studies, gender specific risk factors such as puerperium and oral contraceptive use had favorable outcome. Favorable outcome in gender specific risk factors in CVT has been attributed to that occlusion is limited and transient with rapid recanalization or by development of collaterals [15,16].

According to VENOST study, headache was more common in males while seizures, focal deficit and encephalopathy were common in females. In our study encephalopathy, focal seizures, focal sensory deficit and papilledema were more common in males and headache, GTCs, motor deficit were common in females, which is attributed to the larger sample size in that study (1144 patients). Females were sensitive to pain and it could be expressed emotionally in females than males [16].

In the present study, headache showed significant relationship with poor outcome, while GTCs, motor deficit and encephalopathy showed non-significant relationship with poor outcome. Mohapatra et al. and Duman et al. studies found that focal motor deficit and encephalopathy had a poor outcome. Focal Seizures had no effect on outcome in our study similar to Duman et al., [16,17].

According to our study SSS was the most common affected sinus 65.9% followed by transverse sinus 43.9% that was in agreement with Mangshetty & Reddy study. Superficial cortical veins drain into SSS against the blood flow in the sinus, thus causing turbulence in the blood stream that is further aggravated by the presence of fibrous septa at the inferior angle of the sinus. This fact explains greater prevalence of SSS thrombosis [18,19].

In our study 31% cases had more than one sinus involved that was in agreement with Bousser & Barnett study who found that 40% of cases had more than one sinus was involved. That means that CVT presenting symptoms were non-specific as lead to delay in diagnosis [20].

Ferro et al., stated that ICH on admission CT is associated with poor outcome, that was not obvious in our study mostly due to small sample size and early admission with mild presentations.

Hemorrhage and infarction tend to occur more frequently in the patients with eventually poor outcome, but without significant difference similar to the present study [13,21].

According to Souirti et al., study, 60% of patients showed full recovery, 26% had sequelae and 10% were died while in our study 91% showed complete recovery, 8.6% had sequelae and 14.6% were died. The most common cause of death in our study was herniation (50%). According to Alonso et al., study, death was due to malignancy and infection, that difference because of wide spectrum use of antibiotics and the wide age spectrum of other study [7,22].

#### *Conclusion:*

CVT is more common in females than males. OCP and postpartum state are most common risk factors of CVT patients. Headache is the most common presenting symptoms followed by motor deficit. Motor deficit and encephalopathy are more common in females while papilledema, focal seizures, sensory deficit and aphasia were more in males. D-dimer is positive in about three fourth of patients. Hypercoagulable state and antiphospholipid syndrome are more common in females and hypercoagulable and sepsis in males. The most common sinus affected is SSS followed by transverse sinus and sigmoid sinus and multiple affected sinuses are in about one third of patients. Female sex, GCS less than 10, NIHSS more than 14 and patients presented by headache have poor outcome

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#### *Conflicts of interest:*

No conflicts of interest declared.

#### *Authors' Contributions:*

All authors had equal role in design, work, statistical analysis and manuscript writing. All authors have approved the final article work.

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## الجلطة الوريدية الدماغية : عوامل الخطورة، الأسباب المحتملة والمآل

تمثل الجلطة الوريدية الدماغية ١.٥-١٪ من كل السكتات الدماغية. متوسط عمر المرضى ٣٥-٤٠ حوالى ٧٥٪ من النساء. تتعلق عوامل الخطر المسببة للجلطة الوريدية الدماغية بنوع الجنس واستخدام وسائل منع الحمل والنفاس. قد تحدث الجلطة الوريدية الدماغية بسبب تغيرات فى جدران الأوعية الدموية أو تغيرات فى تدفق الدم مثل فرط لزوجة الدم كما فى جفاف أو تغيرات فى تخثر الدم مثل نقص مادة البروثرومبين يعانى مرضى الجلطة الوريدية الدماغية من أعراض متعددة مثل الصداع وضعف الرؤية واضطراب الوعى وعدم القدرة على تحريك الأطراف.

الهدف من الدراسة: إلى تقييم عوامل الخطورة والأسباب المحتملة والأعراض السريرية وكذلك المعايير التشخيصية المختلفة والمآل الجلطة الوريدية الدماغية.

المرضى وطرق البحث: هذه الدراسة قد أجريت على المرضى الذين تم إدخالهم إلى قسم الأمراض العصبية والنفسية ويبلغ عددهم ٨٢ حالة تم إكتشاف الجلطة الوريدية الدماغية بعد عمل الأشعة لهم وتم تقسيمهم لمجموعتين النساء والرجال فى الفترة بين ديسمبر ٢٠١٥ وديسمبر ٢٠١٦ وقد تم إجراء الآتى لهم: أخذ التاريخ المرضى بالكامل، إجراء الفحص الأكلينيكي والرنين المغناطيسى على أوردة المخ، إجراء التحاليل الروتينية ومتابعة المرضى بعد ثلاث أشهر من تاريخ الدخول فى ذلك تقييم نتائجنا السريرية والفنية باستخدام مقياس رانكين المعدل لدرجة الإعاقة.

الأستنتاج: الجلطة الوريدية الدماغية أكثر شيوعاً فى النساء عن الرجال وحبوب منع الحمل وفترة ما بعد الولادة من أهم عوامل الخطورة فى الجلطة الوريدية.

التوصيات: نحن نوصى بضرورة عمل التحاليل اللازمة والتصوير الطبى لمعرفة أسباب الجلطة الوريدية الدماغية وذلك لأخذ العلاج اللازم ومنع تكرار حدوثها.