

## **Cerebral Vein Thrombosis in St. James's Hospital: Incidence, predisposing factors and sequelae**

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### **Abstract:**

**Background:** Thrombosis of the cerebral veins and sinuses is a cerebrovascular disorder most commonly affecting young adults. Underlying risk factors for cerebral vein thrombosis (CVT) are identified in 85% of patients. This study aims to identify the underlying risk factors in a cohort of patients with a diagnosis of CVT and identify risk of recurrent events.

**Methods:** A retrospective analysis of data from a cohort of 12 patients with a diagnosis of cerebral vein or sinus thrombosis was performed.

**Results:** 12 patients (10 female, 2 male, median age 30.5 years) with cerebral vein or sinus thrombosis were identified. Ten patients (83%) had a known risk factor for CVT. Thrombophilia (genetic or acquired), use of oral contraceptives, pregnancy and post-partum and infection were the most commonly identified risk factors. Two patients (17%) experienced a recurrence of CVT.

**Conclusion:** The mode of presentation of CVT and its risk factors identified here are similar to those described in international studies. No woman with intrapartum CVT has experienced a recurrence thrombosis to date. Further data is required to provide evidence based management guidelines for the subgroup of women who present with CVT during pregnancy and for the group of women with a history of CVT who become pregnant subsequently.

### **Introduction:**

Cerebral vein thrombosis (CVT) is a potentially life threatening form of thrombosis which affects the venous system of the brain. It is one cause of stroke in young adults, predominately young women<sup>1,2</sup>. While it would be likely that the clinical phenotype of CVT in Ireland mirrors the international experience, few data exist. International information is scarce regarding the likelihood of recurrence and optimal management of cerebral vein thrombosis during pregnancy.

The annual incidence of CVT is approximately 3-4 cases per million. The frequency of cerebral vein thrombosis is increased in the peripartum and post partum period to between 12 and 13.1 cases per 100,000 deliveries<sup>1,4</sup>.

Thrombosis of the cerebral veins leads to venous obstruction, followed by local brain oedema and venous infarction. Thrombosis of the major venous sinuses disrupts the circulation of cerebrospinal fluid, causing intracranial hypertension<sup>1</sup> and in most patients, both processes occur simultaneously. The most frequently identified sites of cerebral vein thrombosis are the lateral and sagittal sinuses<sup>1,2</sup>.

A prothrombotic risk factor is identified in 85% of patients with sinus thrombosis<sup>1</sup> and patients with CVT usually have multiple risk factors<sup>2</sup>. Thrombophilic states (both genetic and acquired) and use of the oral contraceptive pill (OCP) are the most commonly identified risk factors. A recent Italian study found that oral contraceptive use is strongly and independently associated with cerebral vein thrombosis. In addition, the combination of a prothrombin gene mutation and use of OCP further

increased the risk of sinus thrombosis<sup>3</sup>. Mechanical causes of sinus thrombosis include head injury, direct trauma to the sinuses or jugular veins, neurosurgical procedures and lumbar puncture<sup>1</sup>. Pregnancy related hypertension and caesarean delivery are associated with intracranial venous thrombosis in the peripartum and post partum period<sup>4</sup>. A significant minority (12.5%) of cases had no known risk factor<sup>2</sup>.

The clinical presentation of cerebral vein thrombosis is highly variable. Severe headache is present in approximately 90% of adult patients with sinus thrombosis. Cerebral lesions and neurological signs develop in between one third and one half of patients and seizures occur in about 40% of patients<sup>1,2</sup>.

CT scanning is useful in the initial assessment and helps exclude other acute cerebral disorders, however CT results may also be normal<sup>1</sup>. While MRI in combination with magnetic resonance venography is the most sensitive imaging technique for the diagnosis of sinus thrombosis<sup>1</sup>, cerebral angiography provides more detailed imagery of the cerebral veins and represents a useful diagnostic tool in cases where CT or MRI results are ambiguous<sup>1</sup>.

The combination of raised intracranial pressure and venous infarction means that patients are at risk of death from cerebral herniation. Management options to prevent or reverse cerebral herniation include administration of intravenous mannitol surgical removal of the infarct or decompressive hemicraniectomy<sup>1</sup>. Anticoagulation with heparin is widely used to halt the progression of the thrombosis and prevent pulmonary embolism<sup>1,2</sup>. However, venous infarcts may become haemorrhagic and the optimal duration of treatment is unknown. Endovascular thrombolysis has been used in some centres.

CVT is associated with significant morbidity and mortality, the latter ranging from 8% to 30%<sup>2,5</sup>. One recent study found that 36% of survivors of CVT had some neurological impairment, though 22% of these were mild<sup>2</sup>. Coma, cerebral haemorrhage and malignancy have been identified as risk factors for death or dependence<sup>2,6</sup>. In the same study, 2.2% of patients suffered a recurrent sinus thrombosis while 4.3% had another thrombotic event<sup>2</sup>.

### **Aim of Study:**

To identify the underlying risk factors in a cohort of patients diagnosed with CVT and to identify the risk of recurrent thrombotic events, particularly in women during pregnancy and in the post-partum period.

### **Methods:**

Data were collected retrospectively from a cohort of 12 patients referred to the National Centre for Hereditary Coagulation Disorders, St. James's Hospital between 1995 and 2005. Patients with a diagnosis of cerebral vein or sinus thrombosis made on CT, MRI or MR angiography were included. Underlying prothrombotic risk factors and precipitating factors were sought.

### **Results:**

**Table 1: Demographic Features of Patient Group**

	<b>Number of Patients</b>	<b>Percentage of Cases</b>
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<b>Female</b>	<b>10</b>	<b>83%</b>
<b>Male</b>	<b>2</b>	<b>17%</b>
<b>Age Range = 13-46 years</b>		
<b>Median Age = 30.5 years</b>		

*(percentages given as the nearest whole number)*

Twelve patients were included in the study, of which 10 cases were female. Median age at diagnosis was 30.5 years, with a range of 13 to 46 years. Demographic data on the patient population is outlined in Table 1. Data on clinical presentation are shown in Table 2 below.

**Table 2: Presenting Symptoms:** *(data available for 11/12 patients)*

<b>Presenting Symptoms</b>	<b>Number of patients</b>	<b>Percentage of Patients</b>
Headache	8	67%
Unilateral Limb Weakness	3	25%
Meningism	2	17%
Cranial Nerve Palsy	2	17%
Seizure	2	17%
Loss of Balance/ Fall	2	17%
Unconsciousness	1	8%
Confusion	1	8%
Visual Loss	1	8%
Sensory Symptoms	1	8%
Vomiting	1	8%

*(percentages given as the nearest whole number)*

**Location of Thrombosis in the Major Cerebral Veins and Sinuses:**

Of the 12 patients in the study one third had thrombosis at a single site and one third had thrombosis with extension to another site. Location of the thromboses is described in Table 3. One third (4 patients) had evidence of underlying cerebral ischemia on imaging, of these 4 patients, only 1 developed long term neurological sequelae (epilepsy).

**Table 3: Location of Thrombosis on Imaging**

*(Data available for 12 patients. Thrombus may affect more than one site)*

<b>Location of Thrombosis</b>	<b>Number of Patients</b>	<b>Percentage of Cases</b>
Superior Sagittal Sinus	6	50%
Transverse sinus (left or right)	7	58%
Jugular Veins	1	8%
Cavernous Sinus	1	8%
Occipital Sinus	1	8%
Central Thoracic Veins	1	8%
Brachial Subclavian	1	8%

*(percentages given as the nearest whole number)*

**Risk Factors:**

Risk factors for cerebral vein thrombosis are summarised in Table 4. Ten of 12 patients (83%) had an identifiable risk factor for CVT. Of these 10 patients with identified predisposing factors, 4 patients had two risk factors and 1 patient had 3 or more risk factors. Thrombophilia screening was performed in 11 cases. Genetic and acquired thrombophilia was found to be the most common risk factor, followed by pregnancy and the post-partum state, infection and use of the OCP. In 2 cases no known risk factor was identified. Oral contraceptive use was identified as a risk factor in 3 cases, in 2 of these, use of the OCP was the only risk factor identified. Pregnancy was a risk factor in 2 cases, where CVT occurred at 31 weeks and 37 weeks gestation respectively. A third case was post partum.

**Table 4: Risk Factors for Cerebral Vein Thrombosis Identified**

*(percentages given as the nearest whole number)*

<b>Risk Factor</b>	<b>Number of Patients</b>	<b>Percentage of Cases</b>
<b>None Identified</b>	<b>2</b>	<b>17%</b>
<b>Thrombophilia</b>	<b>4</b>	<b>33%</b>
<i>Genetic prothrombotic states</i>	<i>3</i>	<i>25%</i>
Protein S deficiency	1	8%
Prothrombin mutation	1	8%
Antithrombin deficiency	1	8%
<i>Acquired prothrombotic states</i>	<i>1</i>	<i>8%</i>
Antiphospholipid antibodies	1	8%
<b>Vasculitis</b>	<b>1</b>	<b>8%</b>
Beçhets disease	1	8%
<b>Pregnancy &amp; post partum</b>	<b>3</b>	<b>25%</b>
<b>Infection</b>	<b>3</b>	<b>25%</b>
Systemic Infection	2	17%
Sinusitis	1	8%
<b>Oral Contraceptive Use</b>	<b>3</b>	<b>25%</b>
<b>Corrected OCP*</b>		<b>50%</b>

*\*Excluding male or pregnant cases. Half of non-pregnant female cases used the contraceptive pill*

#### **Management of Patients with Cerebral Vein Thrombosis:**

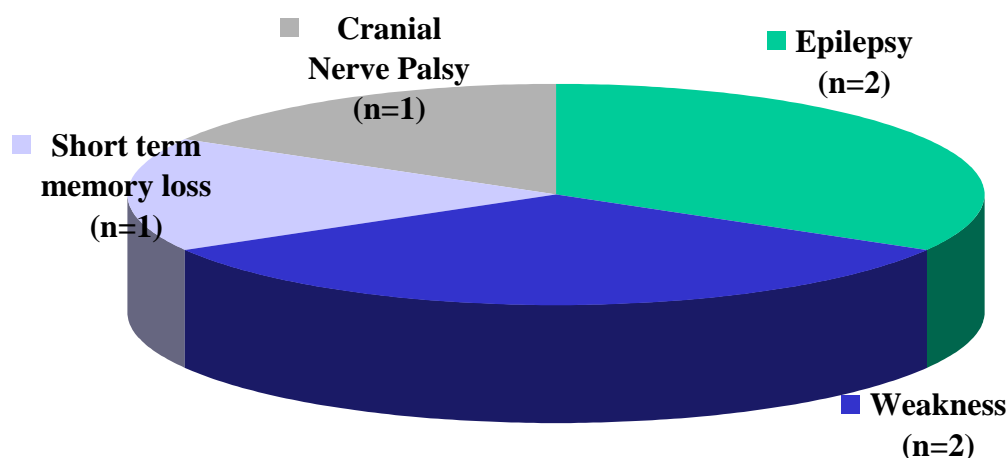
*Data were available for 11 cases.*

All were initially anticoagulated with heparin. One case was given endovascular thrombolysis with urokinase, complicated by the development of a retroperitoneal haematoma. No patients required neurosurgical intervention. Five patients remain on lifelong anticoagulation with warfarin, and three patients remain on lifelong aspirin.

#### **Outcome for Patients with Cerebral Vein Thrombosis:**

Six of the 12 patients developed long term neurological sequelae. The various types of neurological sequelae are outlined in Figure 1 (below). Thrombotic events and seizures occurring during follow-up are outlined in Table 5.

**Figure 1: Long Term Neurological Sequelae**



**Table 5: Events during follow-up**  
(percentages given as the nearest whole number)

	Number of Patients	Percentage of Cases
<b>Recurrent sinus thrombosis</b>	<b>2</b>	<b>17%</b>
<b>Other thrombotic events*</b>	<b>2</b>	<b>17%</b>
Deep vein thrombosis	2	17%
Pulmonary embolus	2	17%
<b>Seizures</b>	<b>2</b>	<b>17%</b>

\* 2 cases developed both deep vein thrombosis and pulmonary embolus

**Cerebral Vein Thrombosis and Subsequent Pregnancy:**

Of the 10 women in our cohort, 3 have had subsequent pregnancies, one of whom has delivered a healthy baby with no recurrent thrombotic events. She received prophylactic heparin during the postpartum period only. The other two women have not yet delivered.

**Discussion:**

This study shows that the St. James's experience with cerebral vein thrombosis is broadly consistent with published work on the topic, where the patient population (83% female, median age 30.5 years) mirrors the international experience<sup>1,2</sup>. Headache was the commonest presenting feature, though at 67% was lower than the 88.8% - 90% reported in previous studies<sup>1,2</sup>. The transverse sinus was the most commonly observed site of thrombosis, followed by the sagittal sinus. These findings are consistent with those described in the International Study on Cerebral Vein and Sinus Thrombosis (ISCVT)<sup>2</sup>. The vast majority (83%) of patients had an identifiable risk factor and half of these had more than one risk factor. Thrombophilia and oral contraceptive use were the most frequently identified risk factors. The use of the OCP has been found to be strongly associated with sinus thrombosis. Moreover, the combination of the prothrombin gene mutation and OCP has been found to increase the risk of cerebral vein thrombosis further<sup>3</sup>. Infection was reported as a risk factor in 25% of St James's cases compared with 12% of ISCVT cases<sup>2</sup>.

No deaths occurred in our cohort. However, our patient population included only cases of CVT who survived the initial event to be referred to the National Centre for Hereditary Coagulation Disorders.

The International Study on Cerebral Vein and Dural Sinus Thrombosis found that following CVT (median follow-up of 16 months), 57.1% of patients had no signs or symptoms, 22% had minor residual symptoms and 7.5% had mild impairments. Moderate residual impairment was found in 2.9% of the patient population and 2.2% were severely handicapped. Six patients (50%) in the St. James's Study had some residual signs and symptoms. Seizures were reported in 17% of St. James's patients following cerebral vein thrombosis, somewhat higher than the 10% reported in the ISCVT. The absence of data on the severity of the neurological sequelae and their impact on the patients living made further comparison of the long-term effects of CVT with previous published studies difficult.

The rate of recurrence of both CVT and other thromboses is higher in this study than that observed in international studies. Both cases with subsequent thrombosis had their initial cerebral vein thrombosis in 1995.

Following their CVT, 5 patients remain on lifelong warfarin while 3 are on aspirin.

The lack of recurrence of CVT during pregnancy is encouraging. However, our sample size was small. Previous CVT, including puerperal cerebral thrombosis is not considered a contraindication to pregnancy<sup>2,7</sup>.

Finally, we have identified a need for a national database of CVT occurring during pregnancy. Little evidence is available to guide management of these patients both during their pregnancy and in the post partum period. Currently, it is uncertain whether they should receive prophylactic heparin during pregnancy.

### **Acknowledgments**

With thanks to Fionnuala ní Ainle, Specialist Registrar in Haematology. This article is based on data presented to the Haematology Association of Ireland in November 2005.

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