

Improvement in the Prognosis of Cerebral Venous Sinus Thrombosis over a 22-Year Period

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ABSTRACT: *Background:* Cerebral venous thrombosis is a rare cause of stroke, with a number of well-defined risk factors. However, there exist few studies that describe trends in the prognosis of this disease over time. *Methods:* A retrospective study was performed on patients diagnosed with cerebral venous thrombosis at the University of Alberta Hospital during two time periods: 1988-1998 (21 patients) and 1999-2009 (40 patients). Signs and symptoms, risk factors, imaging findings, etiologies, treatment modalities, and status at discharge were examined. *Results:* Headache, nausea and vomiting, focal motor deficit, and seizure were the most common signs and symptoms, and active hormonal contraception was the most commonly identified risk factor between the two cohorts. Hematoma and hyperdense sinuses were the most commonly identified CT findings between groups. Thrombophilia and the use of hormonal contraception were the most frequently identified etiologies between the two cohorts. Treatment was similar, with the majority of patients in both cohorts receiving unfractionated heparin as first-line therapy. Patients in the 1999-2009 cohort were significantly less likely to have a severe deficit or be dead at discharge (odds ratio [OR]=0.178; 95% confidence interval [CI_{95%}]=0.051, 0.625) and were more likely to have a favorable modified Rankin Scale score of 0 or 1 at discharge (OR = 7.98; CI_{95%} = 1.79, 35.71). *Conclusions:* Our data indicate a reduction in severe residual symptoms at discharge and improved functional status at discharge for patients presenting with cerebral venous thrombosis from 1999 to 2009, as compared with 1988-1998.

RÉSUMÉ: *Amélioration des pronostics consécutifs à une thrombose des sinus veineux cérébraux au cours d'une période de vingt-deux ans.*

Contexte: Une thrombose des sinus veineux cérébraux, pour laquelle on sait qu'il existe un certain nombre de facteurs de risque précis, demeure une cause inhabituelle d'AVC. Cela dit, il n'existe que peu d'études ayant décrit l'évolution des pronostics se rattachant à cette complication. *Méthodes:* Nous avons mené une étude rétrospective portant sur des patients de l'Hôpital de l'Université de l'Alberta chez qui on avait diagnostiqué une thrombose des sinus veineux cérébraux. Notre étude s'est penché sur deux périodes : 1988-1998 (21 patients) et 1999-2009 (40 patients). Ont été examinés les signes cliniques et les symptômes, les facteurs de risque, les résultats d'examen IRM, les étiologies, les modalités de traitement et la situation des patients au moment d'obtenir leur congé de l'hôpital. *Résultats:* Des maux de tête, des nausées et des vomissements, de même qu'un déficit moteur affectant certaines régions du corps et des convulsions, se sont avérés les signes cliniques et les symptômes les plus répandus. Le fait de suivre de façon active un traitement hormonal de contraception s'est par ailleurs révélé le facteur de risque le plus souvent identifié dans les deux cohortes. De plus, des hématomes et l'hyperdensité des sinus ont été les deux anomalies les plus fréquemment observées, encore une fois dans les deux cohortes, à la suite d'examen tomographiques assistés par ordinateur. La thrombophilie et l'utilisation de contraception hormonale ont été les deux étiologies les plus fréquemment identifiées dans les deux cohortes. En ce qui concerne les modalités de traitement, elles se sont avérées similaires d'une cohorte à l'autre, la majorité des patients bénéficiant d'héparine non fractionnée comme traitement de première intention. Les patients de la cohorte 1999-2009 sont apparus nettement moins susceptibles d'être atteints d'un déficit sévère ou de décéder avant d'obtenir leur congé de l'hôpital (rapport de cotes [RC]=0,178; IC_{95%} = 0,051 ; 0,625) et plus susceptibles d'obtenir un score favorable de 0 ou 1 à l'échelle modifiée de Rankin au moment de quitter l'hôpital (RC = 7,98; IC_{95%} = 1,79 ; 35,71). *Conclusions:* Nos données indiquent ainsi une diminution des symptômes résiduels sévères des patients au moment où ils ont obtenu leur congé de l'hôpital. De plus, les patients de la cohorte 1999-2009 ayant été victimes d'une thrombose des sinus veineux cérébraux ont montré, au moment de quitter l'hôpital, une plus grande amélioration de leur état fonctionnel si on les compare aux patients de la cohorte 1988-1998.

Keywords: Cerebral venous sinus thrombosis, Stroke, Temporal trends, Prognosis

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INTRODUCTION

Gowers¹ was the first to describe cerebral venous thrombosis (CVT) in his seminal work on diseases of the nervous system. Since that time, and in concert with the evolution of novel non-invasive imaging techniques,^{2,3} our knowledge of CVT has greatly expanded. CVT accounts for 0.5% of all strokes,⁴ with an annual incidence of roughly 7 cases per million adults.^{5,6} Of all reported CVT cases, roughly 75% occur in females,^{6,7} likely related to such conditions as pregnancy, puerperium, and the use

of oral contraceptives.^{5,8} Though a large number of additional CVT risk factors have been proposed, recent multicenter studies have helped clarify the most prevalent and critical

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risk factors.^{5-7,9-12} One of the largest studies to date, the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), demonstrated that thrombophilia, puerperium, and infection are the most common risk factors in patients with CVT.⁷

The clinical presentation of CVT is highly variable, with the most common presentation being headache.⁷ A wide range of other symptoms—including focal motor deficits, focal sensory deficits, seizure, encephalopathy, and coma—have been well-described throughout the literature, though all of them lack specificity for CVT.⁶ While clinical presentation and known CVT risk factors can provide clues to the diagnosis of CVT, neuroimaging studies are key to establishing the diagnosis. A variety of imaging modalities—including computed tomography (CT), magnetic resonance imaging (MRI), CT angiography (CTA) and venography (CTV), MR venography (MRV) and contrast enhanced MRV, and digital-subtraction angiography (DSA)—now exist to help confirm the diagnosis of CVT. Of these, MRI with contrast-enhanced MRV is the most sensitive modality for detection of CVT.^{4,13} Guidelines now exist for the treatment of CVT,¹⁴ with a focus on early administration of antithrombotic therapy, aggressive management of raised intracranial pressure, and prompt control of seizures.

Classically, the prognosis of CVT has been grim, what with a mortality rate as high as 50%.^{15,16} However, with the evolution of modern neuroimaging techniques and interventions, in addition to the early administration of antithrombotic therapy, the prognosis of CVT is felt to have significantly improved.^{7,9,17-20} Surveillance studies describing the trends in the prognosis of CVT over time in defined populations are lacking. In the present study, we compare patients diagnosed with nonseptic CVT at the University of Alberta Hospital (UAH) from two time periods (1988-1998 and 1999-2009) in order to better understand the evolution and outcomes of this condition in a Canadian tertiary-care institution.

METHODS

A retrospective study was performed on patients diagnosed with CVT at the UAH during two sequential time periods: 1988-1998 and 1999-2009. The UAH is the only tertiary-care neurological and stroke center in a region with a catchment area of about 1.5 million persons. Patients were included in the study provided they had a diagnosis of nonseptic CVT (with ICD-9 codes 325 and 437.6 and ICD-10 codes I63.6, I67.6, and G08) and were over 18 years of age. From these patients, we included only those with nonseptic cerebral venous sinus thrombosis. All the patients in our study were admitted through the neurology service. The study received ethics approval from the Human Research Ethics Board of the University of Alberta.

Data extraction focused on presenting signs and symptoms; a comprehensive list of risk factors associated with CVT;⁷ imaging findings (including CT, CTA, CTV, MRI, MRA, MRV, and DSA); identified etiologies; treatment modalities; and clinical status at discharge. Discharge-modified Rankin Scale (mRS) score was determined from the allied health (rehabilitation) section on inpatient charts. Severe symptoms at discharge were defined as death, seizures, focal weakness, or language deficit. All data are presented as means \pm standard deviations or percentages. Univariate analysis was performed with chi-square tests, *t*-tests, or Wilcoxon's rank-sum tests where appropriate. Multivariate analysis was undertaken employing logistic regression. Statistical calculations were executed using OriginPro 8[®] (Origin Lab,

Northampton, MA) and SAS 9.3 (SAS Institute, Cary, NC). Results were considered significant when $p < 0.05$.

RESULTS

Twenty-one patients from the 1988-1998 cohort (C1) and 40 patients from the 1999-2009 cohort (C2) were identified as having CVT. There were 19 females (90.5%) and 2 males in C1, whereas there were 22 females (55.0%) and 18 males in C2, and this difference was significant ($p = 0.009$). Age was comparable between the two groups, with the average age of C1 = 35.2 ± 15.9 and C2 = 40.7 ± 15.4 years ($p = 0.195$). There was no significant difference in median time to presentation (C1 = 3 days, interquartile range [IQR] = 1, 6; C2 = 7 days, IQR = 1, 10.5; $p = 0.193$) between the groups. Presenting signs and symptoms were similar between the two cohorts, with the most common being headache, nausea/vomiting, focal motor deficit, and seizure (see Table 1). Seizure at presentation was significantly more common in C1, as compared to C2. The most common identified CVT risk factor in both groups was active hormonal contraception (Table 2). Previous DVT was the only risk factor that was different between the two groups, being more frequent in C2.

Imaging findings were similar between both groups (Table 3). All patients received CT scanning, and in both cohorts the most frequent CT findings were hematoma and hyperdense sinuses. Rare CT findings from C1 included one patient with

Table 1: Presenting symptoms/signs

	1988-1999 (N = 21)	1999-2009 (N = 40)	
Symptom/sign	n (%)	n (%)	p value
Headache	18 (85.7)	30 (75.0)	0.5124
Nausea/vomiting	7 (33.3)	18 (45.0)	0.4234
Papilledema	3 (14.3)	7 (17.5)	1.0000
Proptosis	1 (4.8)	0 (0.0)	0.3443
Focal sensory	3 (14.3)	6 (15.0)	1.0000
Visual defect	1 (4.8)	10 (25.0)	0.0789
Confusion	2 (9.5)	5 (12.5)	1.0000
Agitation	3 (14.3)	2 (5.0)	0.3286
Somnolence	1 (4.8)	7 (17.5)	0.2434
Gait disturbance	0 (0.0)	2 (5.0)	0.5484
Photo/phonophobia	2 (9.5)	6 (15.0)	0.7028
Meningismus	0 (0.0)	2 (5.0)	0.5410
Fever	0 (0.0)	1 (5.0)	1.0000
Cranial nerve findings	2 (9.5)	2 (5.0)	0.6024
Severe symptoms			
Focal motor	11 (52.4)	15 (37.5)	0.2891
Seizure	11 (52.4)	10 (25.0)	0.0475
Stupor	2 (9.5)	2 (5.0)	0.6024
Coma	1 (4.8)	1 (2.5)	1.0000
Death	0 (0.0)	0 (0.0)	1.0000
Aphasia	4 (19.1)	4 (10.0)	0.4291
Any severe symptoms	15 (71.4)	23 (57.5)	0.811

Table 2: Identified risk factors

	1988-1998 (N = 21)	1999-2009 (N = 40)	
Risk factor	n (%)	n (%)	p value
Diarrhea	1 (4.8)	3 (7.5)	1.0000
Dehydration	2 (9.5)	5 (12.5)	1.0000
Previous DVT	0 (0.0)	8 (20.0)	0.0421
Thrombophilia	–	3 (7.5)	N/A
Malignancy	0 (0.0)	6 (15.0)	0.0848
Previous thrombotic events	0 (0.0)	6 (15.0)	0.0848
Pregnant/peripartum	2 (9.5)	3 (7.5)	1.0000
Active hormonal contraception	7 (33.3)	10 (25.0)	0.5545
Active hormone replacement	1 (4.8)	1 (2.5)	1.0000
Active chemotherapy	0 (0.0)	3 (7.5)	0.5449
FMHx of thrombotic event	1 (4.8)	6 (15.0)	0.4047
FMHx of thrombophilia	2 (9.5)	3 (7.5)	1.0000
Active smoker	5 (23.8)	5 (12.5)	0.2912

DVT = deep vein thrombosis; FMHx = family history; N/A = not applicable.

intraventricular hemorrhage (IVH) and another with a dilated superior orbital vein, whereas temporal metastasis was noted in one patient from C2 (data not shown). There were 90.5% (18/21) of patients from the first cohort who received MRI and 87.5% (35/40) in the second. On MRI, sinus thrombus was detected in roughly three-quarters of patients in each cohort. Intracranial hemorrhage (ICH) was also common among the two groups, with approximately 30% of patients in each group demonstrating this finding. Seven C1 patients (33.3%) underwent DSA, all demonstrating the presence of a venous thrombus. A total of 5 patients (12.5%) from the C2 cohort also had a cerebral angiogram. As with C1, all 5 had demonstrated thrombus on cerebral angiogram.

Table 3: CT and MRI findings

CT	1988-1998 (N = 21)	1999-2009 (N = 40)	
Finding	Frequency, n (%)	Frequency, n (%)	p value
Hematoma	7 (33.3)	13 (32.5)	1.0000
Subarachnoid hemorrhage	2 (9.5)	6 (15.0)	0.7028
Hyperdense veins/sinuses	9 (42.9)	24 (60.0)	0.2806
Venous infarct	2 (9.5)	4 (10.0)	1.0000
Edema	3 (14.3)	9 (22.5)	0.5180
MRI	1988-1998 (N = 19)	1999-2009 (N = 35)	
Finding	Frequency, n (%)	Frequency, n (%)	p value
Sinus/venous thrombus	16 (76.2)	31 (77.5)	1.0000
Venous infarct	4 (19.1)	14 (35.0)	0.2461
Intracerebral hemorrhage	6 (28.6)	12 (30.0)	1.0000
Subarachnoid hemorrhage	2 (9.5)	2 (5.0)	0.5987

Table 4: Etiologies

	1988-1998	1999-2009	
Etiology	n (%)	N (%)	p value
Idiopathic	4 (19.1)	17 (42.5)	0.0911
Dehydration	1 (4.8)	4 (10.0)	0.6563
Thrombophilia*	6 (28.6)	5 (12.5)	0.1643
Hormonal medication	5 (23.8)	3 (7.5)	0.1104
Malignancy	0 (0.0)	5 (12.5)	0.1543
Pregnancy/peripartum	1 (4.8)	2 (5.0)	1.0000
Multiple etiologies	4 (19.1)	4 (10.0)	0.4291

*The identified thrombophilias in the 1988-1998 cohort were systemic lupus erythematosus (SLE, one patient); SLE with anti-phospholipid antibody syndrome (antiphospholipid antibody syndrome [APLA], one patient); paroxysmal nocturnal hemoglobinuria (one patient); APLA with protein S deficiency (one patient); factor V Leiden mutation (heterozygous, one patient); and polycythemia rubra vera (one patient). The thrombophilias identified in C2 were protein S deficiency (one patient), APLA (two patients), hyperhomocysteinemia (one patient), and factor V Leiden mutation (one patient).

There was no significant difference between the two groups with respect to CVT etiologies (Table 4). The most common etiologies in C1 were thrombophilia and the use of hormonal medications. In C2, thrombophilia (5 patients, 12.5%) and malignancy (5 patients, 12.5%) were common etiologies, though an etiology was not identified in 17 patients (42.5%). The identified malignancies were breast cancer (3 patients), colon cancer (1 patient), and brain cancer (grade IV astrocytoma, 1 patient).

Anticoagulation with unfractionated heparin or low-molecular-weight heparin was the most common treatment modality between the two cohorts, with 18 patients (85.7%) from C1 and 36 (90.0%) from C2 undergoing this treatment. We found that 71.4% of patients in C1 and 72.5% of C2 patients were also bridged to warfarin during hospitalization. Thrombolytics were rarely used in the treatment of CVT, with only 3 patients (14.3%) in the C1 group and 2 (5.0%) in the C2 group undergoing catheter-based intracranial thrombolysis. Similarly, antiplatelet agents were used in only 9.5% of C1 patients and 15% of C2 patients.

At discharge, 4 patients (19.1%) from the C1 group and 2 patients (5.0%) from the C2 cohort died during the course of hospitalization, but this difference was not statistically significant (Table 5). Ongoing seizure activity at the time of discharge was more common in the C1 cohort, as compared to the C2 cohort. These were continued intermittent seizures, as no patients had partial or generalized status epilepticus. Other individual deficits (including focal motor, focal sensory, and language deficits) were not significantly different between groups at discharge. Patients in the second cohort were significantly less likely to have at least one severe deficit or to have died at discharge, and this difference persisted after adjustment for age and sex (odds ratio [OR] = 0.178; 95% confidence interval [CI]_{95%} = 0.051, 0.625). Similarly, patients in the second cohort were considerably more likely to have a favorable mRS score of 0 or 1 at discharge (Table 5). This difference persisted after adjustment for age and sex (OR = 7.98; CI_{95%} = 1.79, 35.71). The average length of stay was

Table 5: Clinical status at discharge

	1988-1998	1999-2009	
Status	n (%)	N (%)	p value
Death	4 (19.1)	2 (5.0)	0.1688
Seizure	10 (47.6)	5 (12.5)	0.0044
Focal weakness	9 (42.9)	10 (25.0)	0.2440
Language deficit	1 (4.8)	3 (7.5)	1.0000
Vision deficit	3 (14.3)	6 (15.0)	1.0000
Focal sensory	3 (14.3)	2 (5.0)	0.3286
Gait disturbance	1 (4.8)	2 (5.0)	1.0000
Any severe symptoms*	13 (61.9)	9 (22.5)	0.0023**
mRS score of 0 or 1	9 (42.9)	30 (75)	0.0130**

*Severe symptoms at discharge defined as any of death, continuing intermittent seizures, focal weakness, or language deficit.

**This difference persisted after adjustment for age and sex (see Results section).

similar between groups, being 12.0 ± 12.5 days in C1 and 12.5 ± 9.9 days in C2 ($p = 0.449$).

DISCUSSION

To our knowledge, our study represents the longest duration of surveillance for CVT hospitalizations within a defined catchment area to examine for trends in prognosis over time. Our study differs in purpose from such longitudinal studies as the Cerebral Vein Thrombosis International Study (CEVETIS), which took a single large cohort of patients and followed them over time to determine long-term outcomes.²² Similarly, the ISCVT clarified much in the way of our understanding of CVT, though it did not examine trends over time.⁷

Herein we retrospectively studied two cohorts (C1 = 1988-1998, C2 = 1999-2009) of patients diagnosed with CVT at the UAH, so that we might better understand the evolution of presentation and prognosis of this condition at a major Canadian tertiary-care institution. We found diverse etiologies, the most common being thrombophilia, hormonal medications, and malignancy. A number of cases, particularly in the C2 cohort, did not have an identified etiology.

The majority of patients diagnosed with CVT from our study were female. There was a strikingly higher preponderance of female patients in C1 compared to C2. In addition, the number of patients presenting in C2 was double that of C1. The population of Edmonton increased by 16% between the midpoints of the two study periods, which does not account for the discrepancy in numbers. This suggests that the condition may have been underdiagnosed at our institution during the first time period, and particularly among males. Both cohorts had similar rates of CT scan and MRI scan use. Improvements in diagnostic imaging modalities such as contrast-enhanced MRV and better availability of these modalities in the second cohort may have allowed for diagnosis of more patients of lower severity. It is possible that over the time period of the first cohort there were other patients not diagnosed and not included due to false-negative imaging, as a result of sequences that were less advanced than those in the second cohort. This may have produced some degree of ascertainment bias favoring better prognosis in the second cohort.

However, if the differences in outcome were entirely due to ascertainment bias, we would have expected a much greater baseline severity at presentation in the first cohort compared to the second. There did seem to be a trend toward a higher frequency of severe symptoms in the first cohort, who, overall, were 14% more likely to have at least one severe symptom at presentation. However, this difference was not statistically significant. Seizure occurrence was the only presentation variable that was significantly different between the two groups, with seizures being more common in C1. Despite being not significantly different at presentation, patients in C1 had a higher likelihood of being dead or having at least one severe deficit at discharge and were less likely to have a favorable discharge mRS score than those in C2. In contrast to the relatively small 14% discrepancy in severe symptoms at presentation, there was a nearly 40% difference in severe symptoms upon discharge in C1 compared to C2 (Table 5). This implies a greater deterioration over the length of admission of the C1 cohort versus that in the C2 cohort. The reasons for this are not known with certainty, as both cohorts received similar antithrombotic management. We are unable to compare the timing of initiation of anticoagulant therapy between cohorts, as that information was not collected. The C1 cohort patients actually presented an average of 4 days earlier from symptom onset than those in the C2 cohort. Even if we allow for a 1- to 2-day delay in obtaining imaging in C1 compared to C2 due to less timely access, it seems unlikely that anticoagulation would have been initiated longer after presentation in C1 compared to C2. It is likely that other advances in general stroke care at the UAH from 1999 to 2009 may have resulted in improved outcomes.

We found in-hospital mortality to be higher in the C1 group (19.1%) compared to that in the C2 cohort (5%), but this difference was not statistically significant and was based on only 6 deaths. Nonetheless, our combined mortality rate across both cohorts was 10%. The 1988-1998 cohort had a significantly lower proportion of patients with an mRS score of 0 to 1. In contrast, 75% of the patients in the 1999-2009 cohort had an mRS score of 0 to 1. We were not able to detect any differences in investigation, management, and etiology between our two cohorts that could clearly explain the discrepancies in outcome.

STUDY LIMITATIONS AND STRENGTHS

There are several limitations to our study to be noted. This research was retrospective in nature and relied on ICD-9 and ICD-10 codes to identify only CVT patients who were admitted to hospital. We may have missed patients with less severe disease seen in neurological clinics. Where inpatients are concerned, studies suggest that ICD codes have reasonable sensitivity and specificity to detect CVT.²¹ It is therefore unlikely that we missed CVT patients in our target population of those patients severe enough to be admitted to hospital. The small study size is a limitation, and our sample may not provide adequate power to demonstrate statistically significant differences between the two groups. This is a limitation common to studies examining low-incidence conditions. We still consider it worthwhile to obtain regional data on such uncommon conditions as CVT. We discussed above the possibility that patients with milder symptoms in the first cohort may have been missed, and males in particular. Nonetheless, our conclusions still apply to those patients receiving a confirmed diagnosis of cerebral venous sinus

thrombosis at a tertiary-care institution during the time periods in question. Finally, we do not have predmission mRS score available to ensure that differences between mRS score on discharge were not due to preexisting differences. Having said that, the patients in both cohorts were admitted from the community, were quite young on average, and had a similar proportion of severe neurological deficits at presentation, so we think it very likely that they were similar functionally upon preadmission.

Taken together, our data suggest improvements in the number of patients diagnosed, a reduction in severe residual symptoms at discharge, and improved functional status at discharge for patients presenting with CVT from 1999 to 2009 compared to patients from the time period of 1988-1998.

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STATEMENT OF AUTHORSHIP

TJ designed the study. JK and TJ performed the chart review. DA and TJ performed data analysis and wrote the manuscript.

DISCLOSURES

Drs. Anderson and Kromm contributed equally to this work. They both hereby declare that they have nothing to disclose.

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