

Epileptic Seizures In Cerebral Venous Sinus Thrombosis: Subgroup Analysis Of VENOST Study

Cover Title: Early Seizures in Cerebral Venous Thrombosis

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Highlights

- In our study, approximately one-fourth of patients with CVST had early seizures.
- Female sex, presence of focal neurological deficits, altered consciousness were risk factors.
- Superior sagittal sinus and cortical veins thrombosis and hemorrhagic infarction were associated with seizures.
- The outcome in the first month was worse.
- But the long-term prognosis was good in epileptic seizures group.

Abstract

Purpose: The aim of this study is to evaluate the presence and prognostic impact of early seizures in cerebral venous sinus thrombosis patients (CVST).

Method: VENOST is a retrospective and prospective national multicenter observational study. CVST patients with or without epileptic seizures (ES) were analyzed and compared in terms of demographic and imaging data, causative factors, clinical variables, and prognosis in a total of 1126 patients.

Results: The mean age of the patients in the ES group was 39.73 ± 12.64 and 40.17 ± 14.02 years in the non-ES group ($p > 0.05$). Epileptic seizures were more common (76.6%) in females ($p < 0.001$). Early ES occurred in 269 of 1126 patients (23.9%). Epileptic seizures mainly presented in the acute phase (71.4%) of the disease ($p < 0.001$). Majority of these (60.5%) were in the first 24 hours of the CVST. The most common neurological signs were focal neurologic deficits (29.9%) and altered consciousness (31.4%) in the ES group. Superior sagittal sinus (SSS) and cortical veins (CV) involvement were the most common sites of thrombosis and the mostly related etiology were found puerperium in seizure group (30.3% vs 13.9%). Patients with seizures had worse outcome in the first month of the disease ($p < 0.001$) but these did not have any influence thereafter.

Conclusions: In this largest CVST cohort (VENOST) reported female sex, presence of focal neurological deficits and altered consciousness, thrombosis of the SSS and CVs, hemorrhagic infarction were risk factors for ES occurrence in patients with CVST.

Keywords: Cerebrovascular disease, cerebral venous sinus thrombosis, epilepsy, early seizure

1. Introduction

Cerebral venous sinus thrombosis (CVST) is a rare type of cerebrovascular disease, which accounts for only 0.5-1% of all strokes in all age groups (1) and affects mainly young to middle-aged adults (2). The main clinical presentations of CVST include progressive headache, focal neurological deficit, epileptic seizure (ES), and disturbance of consciousness (2).

Epileptic seizures are a common clinical manifestation of CVST (3-5).

Approximately 35-40% of CVST patients experience ESs (6-8). It may occur early or late in the disease process (5,6).

According to the pooled analysis of the VENOST (3), ISCVT (7) and other studies (5), focal motor deficits, supratentorial parenchymal lesions, cortical vein (CV) and superior sagittal sinus (SSS) are major risk factors of ESs. Epileptic seizures may adversely affect prognosis, CVST patients with ES has three times higher mortality than those without ESs (6).

In the present study, we analyzed the national multicenter study (VENOST) patient data to evaluate the presence and the prognostic effects of early seizure in cerebral venous sinus thrombosis patients.

2. Methods

The methodology for the Multicenter Study of Cerebral Venous Thrombosis (VENOST) has been described in detail in the previous published study (9). This study includes all participants of the VENOST cohort. VENOST is a retrospective and prospective multicenter observational study that includes 1144 patients with CVST diagnosed at 35 centers nationwide. The diagnosis of VENOST was confirmed based on both the clinical presentation of patients and of thrombosis in cerebral venous sinuses on cranial computerized tomography (CT scan), magnetic resonance imaging (MRI), MR venography (MRV) and/or cerebral angiography (DSA) according to established diagnostic criteria (10). The diagnosis of CVST was made according to the American Heart Association / American Stroke Association (AHA/ASA) published a Scientific Statement in 2011 (11). The study was approved by ethical committee of the coordinating center (No: 83045809/604/02-12333).

The patients with past history of seizure, mental retardation, febrile seizure, and associated structural lesions other than CVST were excluded. Patient demographics, past medical history, clinical features, seizure type, laboratory tests, neuroradiological findings and presence

and type of parenchymal lesions (i.e. hemorrhage vs. venous infarcts,) and the modified Rankin score (mRS) at discharge were recorded.

Presenting symptoms and a detailed medical history including deep venous thrombosis (VT), oral contraceptive use, pregnancy, central nervous system or systemic infectious disease, dehydration, malignancy, Behcet's disease, vasculitis, anemia and prothrombotic conditions were also recorded.

Neurological examination was done by local neurologist. Determination the types of sinus thrombosis and the affected regions in the brain were reported by the local radiologist

The onset of CVST was categorized as acute, subacute, and chronic. Type of onset was considered to be acute if duration of symptoms was less than 48 hours on admission, subacute if duration was between 48 hours and 1 month, and chronic if symptom duration was longer than 1 month. This type of classification can be made in neuroimaging studies. The signal of venous thrombi on MR can vary according to the age of the thrombus (acute, subacute, chronic) . In the acute phase, before 3 days after symptoms onset, the signal is isointense on T1-WI and hypointense on T2-WI. But it is difficult to visualize of the thrombus at the acute phase. The thrombus can be mistaken for imaging artifacts, such as; low flow of normal venous blood, hypoplasia or atresia, arachnoid granulations, anatomical variations. In the subacute phase (after three days), it is hyperintense on on all sequences (T1, T2, FLAIR, T2*, diffusion). It the chronic phase (after one month), it depends on the degree of organization of the clot. It becomes isointense on T1-WI, iso-/hyperintense on T2-WI, and hypointense on T2*(12).

The diagnosis of CVST is typically based on a clinical suspicion and imaging confirmation. But

in some patients, the duration of symptoms is not match with the thrombosis formation time.

It is thought that the progression of thrombus formation may lead to severe focal neurologic

deficits, coma, or death.

The most accurate classification for epileptic seizure is referred to Ferro et al., who assorted seizures into 3 groups including presenting seizures (before diagnosis of CVST), early seizures (within 14 days of diagnosis of CVST), and late seizures (after 14 days of diagnosis of CVST). But most of the studies have used the terms “acute” for both presenting and early seizures and “remote” for late seizures.

Statistical analysis

The baseline characteristics of the patients with or without ESs were compared by student unpaired t- test for continuous variables and chi square test for categorical variables. Univariate Anova test was used for the predictors of ESs; including the demographic, clinical, risk factors, imaging findings and etiology. Significant probability value (p value) was considered to be <0.05). Statistical analyses were performed using SPSS software (version 17).

3. Results

One thousand one hundred twenty-six consecutive patients out of 1144 patients with CVST were included in the study. Eighteen patients were excluded due to missing CVST or ESs onset data. Patients were divided into 2 groups comprising of patients with and without ESs. Two hundred sixty-nine patients had a history of ESs. The mean age of the patients in the ES group was 39.73 ± 12.64 and 40.17 ± 14.02 years in the non-ES group ($p > 0.05$). Epileptic seizures were more common (76.6%) in females ($p < 0.001$). Patient baseline characteristics are given in (Table 1).

In the ESs group, the onset of CVST was acute in 71.4%, subacute in 18.2% and chronic in 10.4% of the patients. Epileptic seizures mainly occurred in the acute phase of symptom onset in our study group (**Table 1**).

The most common symptoms and clinical signs were focal neurologic deficits (29.9%) and altered consciousness (31.4%) in the ESs group, whereas headache (92.7%), visual field deficits (31.3%) and cranial nerve palsies (12.7%) were more common in the non-ESs group (**Table 1**).

Hemorrhagic infarction was seen in 97 (35.8%) and intracerebral hematoma in 16 (5.9%), infarct in 76 (28.4%) and no lesions in 80 (29.9%) patients in the ES-group whereas 101 (11.6%), 27 (3.1%), 141 (16.2%) and 604 (69.2%) patients in non-ES group respectively (**Table 2**).

We did not find any differences between two groups in terms of multiple venous sinus involvement (**Table 2**), but there was a difference in the location of sinus/vein involvement between the 2 groups. SSS and CV involvement were more common in the ES-group, whereas sigmoid sinus and transverse sinus involvement was more common in the non-ES group (**Table 2**).

Prothrombotic conditions are etiological factors for CVST and we found that only Factor V Leiden mutation (FVL) showed a difference between groups, which was higher in ES groups.

For etiological factors, puerperium is the leading cause in patients with ESs followed by Factor V Leiden mutation (FVL) (**Table 3, Table 4**). The negative impact of ESs on clinical outcome was limited to the 1st month of CVST (**Table 5**).

4. Discussion

In this national multicenter observational study, we found that female sex, focal neurologic deficit and/or altered consciousness at onset, SSS and CVs involvement, hemorrhagic infarction were predictors of ESs.

In our study, the mean age of our patients was 39.73 ± 12.64 , which was similar as reported by the ISCVT and the VENOPORT studies (3,4).

Epileptic seizures are more specific to CVST than patients with hemorrhagic or ischemic strokes (13-15). A meta analysis of observational studies which was published in November 2019 by Li et al, showed 532 (42.7%) patients developed presenting or acute seizures out of the 1244 patients. According to results of this database, early onset seizures have a high incidence in CVST patients (16). We found that 23.9% of patients with CVST had ESs in our study which was lower than the incidence reported in most of the previous studies (6-8). According to different studies ESs develop in 19-65% of CVST cases (17-21).

Predictors of acute seizures included altered consciousness ($GCS < 8$), focal neurological deficit(s), hemorrhagic infarction, frontal lobe involvement, supratentorial lesions, SSS and CVs thrombosis (22). Pregnancy and puerperium have been associated with a very high percentage of seizures in some studies but not others (14,23).

Seizures can develop during different periods of the disease course. It can be categorized as acute seizure (AS), or remote seizures (RS). Acute seizures take place before the diagnosis or during the first 2 weeks afterward. Epileptic seizures are commonly reported to occur in the first year after CVST (17). In different cohorts, it was found that 12-31.9% of patients with CVST have ESs as the presenting symptom (13). In previous studies by Ferro and Masuhr,

early symptomatic seizures were found in 34% and 44.3% patients respectively (4,5). with 44.3% of them occurring in the acute phase. In the present study, we found early ES in 269 of 1126 patients (23.9%) with 71.4% in the acute phase of the disease ($p < 0.001$).

Davoudi et al, found that acute seizures were more common in patients who had paresis, patients who had hemorrhagic and/or supratentorial (especially frontal and parietal lobes) lesions, and in patients with, thrombophilia and/or a history of miscarriage (17). Supratentorial lesions were the most significantly associated factor with occurrence of ASs. Lesions in the parietal lobe were also highly associated with acute phase seizures. Davoudi et al stated that lesions in the one lobe were significantly related with acute symptomatic seizures where as lesions more than one lobe showed no association (17). Acute seizures were the most significant factor associated with remote seizure. Thrombosis in the sigmoid sinus was the only type of sinus significantly associated with RS occurrence. They found no relationship neither acute nor remote seizure nor death (17).

Pregnancy and puerperal CVST have been associated with a very high percentage of seizures in some studies (14,23). Hüseyinoglu et al had found that supratentorial lesion, sagittal sinus thrombosis and puerperal CVST were associated with presenting seizures. (22).

Ferro and Kalite found supratentorial lesions were associated with nearly 5 times higher risk of seizure in their studies. In different studies, the lesions which were located in frontal, parietal and temporal lobes, had a tendency for seizure occurrence (4,7,18).

Epileptic seizures are associated with damage to the motor cortex and surrounding cortical tissues. CVST occurs most often in the SSSs, followed by the transverse and sigmoid sinuses (2, 24).

In the present study we also found that, SSS and CVs involvement were the most common sites of thrombosis in seizure patients and the related causative factors were found puerperium in ESs group (30.3% vs 13.9%). The cortical vein and SSS drain blood from supratentorial parenchyma, involvement of these veins may cause cortical edema by blocking venous drainage (19,20).

Mortality is lower in CVST than in arterial thrombosis. Most CVST patients have a good prognosis. With the help of improvements in treatment and diagnostic technologies, the mortality rate decreased over time (25). Previous studies have shown that 60-79% of patients achieve good functional outcome (mRS 0-1) (7, 26). In our study approximately 80% of patients have mRS of 0-1 in non-ES group and 68% in ES group. The effects of seizures on CVST prognosis is conflicting. Some studies have reported higher functional disability and mortality in patients with seizures, whereas in other studies found no association with a worse outcome (27). In our study, The effects of seizure on prognosis reached statistical significance in the 1st month of the disease ($p < 0.001$) and did not have an effect after the 1st month. So the first month was important for follow the seizure prognosis.

Limitations of the presented study are the lack of data on dosage and type of anti epileptic drugs, type of seizures, EEG findings and incidence of status epilepticus.

CVST can present with slowly progressive symptoms that may account for delays in diagnosis. In the absence of ESs, the routine use of AED in patients with CVT is not recommended.

5. Conclusion

This study is the largest CVST study until that time and we found that approximately one-fourth of patients with CVST had early seizure. Female sex, presence of focal neurological

deficits and altered consciousness, thrombosis of the SSS and CVs, and hemorrhagic infarction were more frequent in patients with acute seizures. The outcome in the first month was worse but the long-term prognosis was good in ESs group.

In conclusion, acute seizure in CVST can cause neurologic and systemic deterioration, status epilepticus and death. Delayed diagnosis of CVST causes mortality and morbidity in patients, standard treatment is still important for CVST.

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Table 1: Demographic data and symptom features of patients with seizures and without seizures of CVST.

Demographic features		Non-ES group n= 857	ES group (+) n= 269	p
Age		40.17±14.02	39.73±12.64	0.621
Gender	Female	559 (%65.2)	206 (76.6%)	<0.001
	Male	298 (%34.8)	63 (23.4%)	
Symptoms onset	Acute	338 (39.4%)	192 (71.4%)	<0.001
	Subacute	334 (39.0%)	49 (18.2%)	
	Chronic	185 (21.6%)	28 (10.4%)	
Symptoms	Isolated Headache	281 (32.8%)	1 (0.4%)	<0.001
	Headache	809 (92.7%)	187 (69.4%)	<0.001
	Nausea and/or Vomiting	248 (28.9%)	65 (24.0%)	0.117
	Visual field defect	273 (31.3%)	30 (11.1%)	<0.001
	Focal neurological deficit	124 (14.5%)	80 (29.9%)	<0.001
	Altered consciousness	117 (13.6%)	85 (31.4%)	<0.001
	Cranial nerve palsies	109 (12.7%)	17 (6.3%)	0.003

Table 2: Affected sinus and paracyhmal involvement in patients with and without seizures.

	Venous sinus involvement	Non-ES group n= 857	ES group (+) n= 269	p
	Transverse sinuses	235 (27.4%)	53 (19.6%)	0.010
	Sagittal sinuses	117 (13.6%)	49 (18.1%)	0.071
Isolated	Sigmoid sinuses	28 (3.3%)	8 (3.0%)	0.764
	Cortical veins	9 (1.1%)	14 (5.2%)	<0.001
	Jugular sinuses	11 (1.3%)	5 (1.8%)	0.552
	Cavernous sinuses	9 (1.0%)	0 (0.0%)	0.126
	Transvers sinuses	647 (75.5%)	180 (66.8%)	0.005
	Sigmoid sinuses	355 (41.4%)	93 (34.7%)	0.050
Multiple involvement	Sagittal sinuses	309 (36.1%)	130 (48.0%)	<0.001
	Internal jugular vein	134 (15.6%)	42 (15.5%)	0.975
	Cortical veins	21 (2.4%)	21 (7.7%)	<0.001
	Cavernous sinuses	16 (1.9%)	2 (0.7%)	0.274
Paracyhmal involvement	No lesion	593 (69.2%)	80 (29.9%)	<0.001
	Infarction	138 (16.2%)	76 (28.4%)	
	Hemorrhagic infarction	99 (11.6%)	97(35.8%)	
	Intracerebral Hemorrhage	27 (3.1%)	16 (5.9%)	

Table 3: Prothrombotic features of patients with and without seizures.

Prothrombotic conditions	Non-ES group n= 857	ES group (+) n= 269	p
MTHFR heterozygote	26 (4.8%)	11 (5.8%)	0.354
MTHFR homozygote	38 (7.0%)	8 (4.2%)	
Phrothrombin mutation	12 (2.2%)	7 (3.7%)	0.291
PAI-Mutation (n=729)	10 (1.9%)	0 (0.0%)	0.071
Factor V Leiden Mutation	22 (4.1%)	15 (7.9%)	0.037
Antiphospholipid Ab	9 (1.3%)	2 (0.9%)	0.742
Hyperhomosisteinemia	32 (4.5%)	13 (5.6%)	0.488
Hyperfibrinogenemia	3 (0.4%)	0 (0.0%)	0.580
Protein C/ S deficiency	32 (4.5%)	15 (6.5%)	0.229
Activated Protein C resistance	11 (1.5%)	3 (1.3%)	0.785
Antithrombin III deficiency	2 (0.3%)	3 (1.3%)	0.098
High ANA titration	13 (1.8%)	8 (3.5%)	0.145
Thrombocytosis	8 (1.1%)	2 (0.9%)	0.737
Anticardiolipin Ab	5 (0.7%)	1 (0.4%)	0.653
Polistemia Vera	7 (1.0%)	0 (0.0%)	0.204

Table 4: Etiological factors in patients with seizures and without seizures

Etiology		Non-ES group n= 857	ES group (+) n= 269	p
Gynecological causes	Oral contraceptive (n=777)	79 (13.9%)	29 (13.9%)	0.983
	Pregnancy (n=777)	56 (9.8%)	18 (8.7%)	0.617
	Puerperium (n=777)	79 (13.9%)	63 (30.3%)	<0.001
Infections	Paracranial (focal)	51 (6.0%)	18 (6.6%)	0.448
	Systemic	20 (2.3%)	3 (1.1%)	
Prothrombotic conditions		230 (26.8%)	90 (33.5%)	0.213
History of VTE	Cerebral	18 (2.1%)	8 (3.0%)	0.676
	Deep venous thrombosis	28 (3.3%)	12 (4.4%)	
	Other	6 (0.7%)	2 (0.7%)	
Malignancy		43 (5.0%)	15 (5.5%)	0.748
Family history VTE		7 (0.8%)	4 (1.5%)	0.475

Table 5: Prognosis of patients with seizures and without seizures

	mRS	Non-ES group n= 857	ES group (+) n= 269	p
1 st month (n=1004)	0-1	619 (81.7%)	168 (68.3%)	<0.001
	2	82 (10.8%)	35 (14.2%)	
	≥3	57 (7.5%)	43 (17.5%)	
3 rd month (n=859)	0-1	582 (90.1%)	182 (85.4%)	0.078
	2	39 (6.0%)	15 (7.0%)	
	≥3	25 (3.9%)	16 (7.5%)	
6 th month (n=778)	0-1	539 (92.5%)	173 (88.7%)	0.250
	2	24 (4.1%)	13 (6.7%)	
	≥3	20 (3.4%)	9 (4.6%)	
12 th month (n=691)	0-1	488 (94.0%)	155 (90.1%)	0.188
	2	15 (2.9%)	7 (4.1%)	
	≥3	16 (3.1%)	10 (5.8%)	