Acute symptomatic seizures in cerebral venous thrombosis

Lindgren E, MD[1,*], Silvis SM, MD[2,*], Hiltunen S, MD, PhD[3], Heldner MR, MD, MSc[4], Serrano F, MD[5], De Sciscio M, MD[6], Zelano J, MD, PhD[1], Zuurbier SM, MD, PhD[2], Sánchez van Kammen M, MD[2], Mansour M, MD[7], Aguiar de Sousa D, MD, MSc, PhD[8], Penas S, B.Hlth.Sci[9], Al-Asady S, MD[10], Ekizoglu E, MD[11], Redfors P, MD, PhD[1], Ahmed A, MD[1], Yesilot N, MD[11], Ghiasian M, MD[7], Barboza MA, MD[12], Arnao V, MD, PhD[13], Aridon P, MD[13], Punter MNM, MD, PhD[10], Ferro JM, MD, PhD[8], Kleinig T, MD, PhD[6], Arauz A, MD, PhD[5], Tatlisumak T, MD, PhD[1, 3], Arnold M, MD[4], Putaala J, MD, PhD[3], Coutinho JM, MD, PhD[2,**], Jood K, MD, PhD[1,**]

[*,**] These authors contributed equally to the manuscript.

1. Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg and Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden

2. Department of Neurology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

3. Department of Neurology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

4. Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland

5. National Institute of Neurology and Neurosurgery Manuel Velasco Suarez, Mexico-City, Mexico

6. Department of Neurology, Royal Adelaide, Hospitals and Department of Medicine, University of Adelaide, Adelaide, SA, Australia

7. Sina Hospital, Hamadan University of Medical Science, Hamadan, Iran

8. Department of Neurosciences and Mental Health (Neurology), Hospital de Santa Maria/CHULN; University of Lisbon, Lisbon, Portugal

9. Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

10. Manchester Centre for Clinical Neurosciences, Salford Royal NHS Foundation Trust, Manchester, United Kingdom

11. Department of Neurology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

12. Neurosciences Department, Hospital Dr. R.A. Calderón Guardia, CCSS, San José, Costa Rica

13. Department of Biomedicine, Neuroscience and Advanced Diagnostics (Bi.N.D),

University of Palermo, Palermo, Italy

Correspondence to: Turgut Tatlisumak, MD, PhD, turgut.tatlisumak@neuro.gu.se

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Abstract

Objective: To identify characteristics, predictors, and outcomes of acute symptomatic seizures (ASS) in cerebral venous thrombosis (CVT), we investigated 1,281 consecutive adult patients with CVT included from 12 hospitals within the International CVT Consortium.

Methods: We defined ASS as any seizure between symptom onset and seven days after diagnosis of CVT. We stratified ASS into pre-diagnosis and solely post-diagnosis ASS. Status epilepticus (SE) was also analyzed separately. We analyzed predictors for ASS, and association between ASS and clinical outcome (modified Rankin Scale) with multivariable logistic regression.

Results: Of 1,281 eligible patients, 441 (34%) had ASS. Baseline predictors for ASS were intracerebral hemorrhage ([ICH], adjusted odds ratio [aOR] 4.1, 95% confidence interval [CI] 3.0-5.5), cerebral edema/infarction without ICH (aOR 2.8, 95%CI 2.0-4.0), cortical vein thrombosis (aOR 2.1, 95%CI 1.5-2.9), superior sagittal sinus thrombosis (aOR 2.0, 95%CI 1.5-2.6), focal neurological deficit (aOR 1.9, 95%CI 1.4-2.6), sulcal subarachnoid hemorrhage (aOR 1.6, 95%CI 1.1-2.5) and female-specific risk factors (aOR 1.5, 95%CI 1.1-2.1). Ninety-three (7%) patients had solely post-diagnosis ASS, best predicted by cortical vein thrombosis (positive/negative predictive value 22%/92%). Eighty (6%) patients had SE, independently predicted by ICH, focal neurological deficits and cerebral edema/infarction. Neither ASS nor SE were independently associated with outcome.

Conclusion: ASS occurred in 1/3 of patients with CVT and was associated with brain parenchymal lesions and thrombosis of the superficial system. In absence of pre-diagnosis ASS, no subgroup was identified with sufficient risk of post-diagnosis ASS to justify

prophylactic antiepileptic drug treatment. We found no association between ASS and outcome.

Introduction

Acute symptomatic seizures (ASS) are reported in 24-50% of patients with cerebral venous thrombosis (CVT) and can occur either before (pre-diagnosis ASS) or after CVT diagnosis (post-diagnosis ASS).[1-3] Various risk factors for ASS have been identified, including focal neurological deficits, supratentorial parenchymal lesions, intracerebral hemorrhage (ICH), focal edema/ischemic infarction, superior sagittal sinus thrombosis, cortical vein thrombosis, and pregnancy or puerperium.[2,4-8] However, data from large international cohorts are scarce and little is known about the risk of developing status epilepticus (SE).[1,9] Although ASS may increase the risk of early death,[5] occurrence of ASS has not been shown to be associated with poor long-term clinical outcome after CVT.[1,9,10]

To prevent further seizures, anti-epileptic drug (AED) treatment is recommended by the European and American guidelines on CVT in patients with ASS and supratentorial lesions.[9,11] However, in the group of patients without seizures at the time of CVT diagnosis, no specific group has been identified with a high enough risk of subsequent post-diagnosis ASS to warrant primary prophylactic AED treatment.[2,4,5,9,11]

The aims of the current study were 1) to confirm previously identified risk factors and search for novel risk factors for ASS in a large cohort of CVT patients, 2) to investigate predictors for post-diagnosis seizures in the absence of pre-diagnosis seizures, in order to identify subgroups potentially benefitting from prophylactic AED treatment, 3) to investigate risk

factors for the development of SE in the acute phase, and 4) to study the association between

ASS and clinical outcome.

Methods

Study design and patient selection

We used data from the International CVT Consortium, which is an ongoing collaboration

between CVT research groups from 12 hospitals.[12-14] Details of the consortium are described

in the Supplemental data available from Dryad (Table e-1 doi:10.5061/dryad.w6m905qm7). Start

of recruitment varied per hospital, the earliest being January 1990. We included adult patients

diagnosed with CVT until December 2018. Patients with a history of epilepsy, eclampsia, or

pre-eclampsia were excluded.

Data collection and definitions

Data on demographics, type of symptom onset, baseline clinical characteristics, risk factors

for thrombosis, laboratory investigations, imaging findings, treatment, and clinical outcome

were recorded using a standardized case record form. Diagnosis of CVT was confirmed with

CT-venography, MRI with MR-venography, catheter angiography, or autopsy, in accordance

with international guidelines.[11] We considered female-specific risk factors as any of the

following: oral contraceptive use, hormone replacement therapy, pregnancy, or puerperium.

Type of onset was categorized according to time from symptom onset to admission as acute

onset (<48 hours), subacute onset (between 48 hours and 30 days), and chronic onset (>30 days).

Seizures were diagnosed by treating physicians. We defined ASS as any seizure that occurred between symptom onset and seven days after diagnosis of CVT.[15,16] We categorized seizures in accordance with the recommendations of the International League Against Epilepsy (ILAE) as focal or bilateral tonic-clonic seizures. We classified focal to bilateral tonic-clonic seizures as bilateral tonic-clonic seizures.[17] Further, we defined SE as continuous seizure activity for five minutes or more, or multiple seizures within 30 minutes without normalization of consciousness in-between.[18] Number of seizures was recorded as single or multiple and seizure recurrence was recorded up to seven days after diagnosis.

Patients with ASS were further subdivided according to the timing of the *first* seizure. Patients in whom the first seizure occurred prior to diagnosis of CVT were categorized as pre-diagnosis ASS, while patients in whom the first seizure occurred after diagnosis of CVT were categorized as post-diagnosis ASS.

With regard to the categorization of baseline radiological findings, intraparenchymal hemorrhages and hemorrhagic infarcts were clustered as intracerebral hemorrhage (ICH). The presence of cerebral edema/infarction without hemorrhage, subarachnoid hemorrhages (SAH), and subdural hematoma (SDH) were scored separately. We recorded the location of the intracerebral lesions as supratentorial and/or infratentorial, and cortical and/or subcortical.

Outcome was assessed using the modified Rankin Scale (mRS) and poor clinical outcome was defined as a score of 2 to 6. For the outcome analysis we used the mRS score at last follow-up. Mortality was also analyzed separately. Patients who were followed-up for less than three months were excluded, except if they had died within three months. The Adelaide cohort did

not collect functional outcome at follow-up and these patients were therefore excluded from the outcome analysis.

Standard Protocol Approvals, Registration, and Patient Consents

Each center received permission from local authorities and ethics committees to collect observational data, and obtained written informed consent, when this was required under applicable national laws.

Data Availability

All study data are available upon reasonable request.

Data analysis

We compared demographic, clinical features, risk factors for CVT, and imaging findings between patients with and without ASS. Associations between baseline characteristics and ASS were investigated using Fisher's exact test for dichotomous data and Mann Whitney U test for continuous data. We assessed potential predictors for ASS using multivariable logistic regression analysis. Three variables (supratentorial lesion, subcortical lesion and cortical lesion) were not considered eligible for multivariate analyses due to more than 5% missing data. Potential predictors were selected based on clinical plausibility and the univariable analysis (p-value <0.1): age, female sex, ICH, cerebral edema/infarct only, focal neurological deficit, sulcal SAH, superior sagittal sinus thrombosis, female-specific risk factor, and cortical vein thrombosis. An identical approach was used in three separate analyses with 1) post-diagnosis ASS, 2) SE, and 3) poor clinical outcome (mRS 2 to 6 at last follow-up at least

three months after CVT diagnosis) as the dependent variables. For analysis on clinical

outcome, we adjusted for factors associated with poor outcome in univariate analysis or

previous literature;[1] age, female sex, focal neurological deficits, coma, infection, ICH,

subdural hematoma, sulcal SAH, and cancer. Odds ratios (OR) and 95% confidence intervals

(CI) were calculated. We compared clinical outcome between patients with pre-diagnosis

ASS and patients with post-diagnosis ASS. We calculated positive predictive values (PPV)

and negative predictive values (NPV) for post-diagnosis ASS separately for all variables with

probability value below 0.1 in univariate analyses. We also performed a sensitivity analysis

including ASS up to 14 days.[2,4-7] All data were analyzed with IBM SPSS Statistics 23.0

(International Business Machines Corporation, New York).

Results

There were 1,308 adult patients diagnosed with CVT within the study period. After applying

the exclusion criteria, 1,281 patients were included in the study (Figure 1). In total, 441 (34%)

patients had at least one ASS and of these, 348 patients (27% of all patients, 79% of patients

with ASS) had pre-diagnosis and 93 (7% of all patients, 21% of patients with ASS) had solely

post-diagnosis seizures. Focal seizures occurred in 187 (15%) patients and tonic-clonic

seizures in 325 (25%) patients. In total, 266 patients (21% of all patients, 60% of patients with

ASS) suffered a recurrent ASS. Of eligible patients, data of 822 patients (64%) were collected

prospectively and 459 patients (36%) retrospectively.

Baseline characteristics of patients with ASS and patients without ASS are presented in Table

1. Patients with ASS were more often of female sex and had more frequently acute onset,

focal neurological deficits, or coma on admission. On baseline imaging, ICH, cerebral

edema/infarction, sulcal SAH, and superior sagittal sinus thrombosis were more common

findings among patients with ASS. Patients with ASS more often had supratentorial or cortical lesions compared to patients without ASS. Patients with ASS also had longer hospital stays, were more often admitted to an intensive care unit and were more often treated with anticoagulants. Among patients with ASS, 161 (37%) patients received acute treatment with benzodiazepines and 217 (49%) received intravenous AEDs. General anesthesia was administered in 61 (14%) patients. Treatment with an AED was started in 410 patients (94%) with ASS, most commonly phenytoin, levetiracetam or valproic acid (Table 1). Six of the patients who had ASS (1%) had received prophylactic AED treatment before the first ASS. Among patients without ASS, two patients (<1%) received prophylactic AED treatment.

Predictors of ASS

In the multivariable model, presented in Table 2, independent predictors of ASS were ICH, cerebral edema/infarct only, cortical vein thrombosis, superior sagittal sinus thrombosis, focal neurological deficits, sulcal SAH, and female-specific risk factors. An additional explorative analysis including ASS up to 14 days post CVT diagnosis yielded the same predictors and only gave a slightly higher estimate of the frequency of ASS, namely 35% (data available from Dryad [Tables e-2 and e-3 doi:10.5061/dryad.w6m905qm7]).

Post-diagnosis seizures

There were 93 patients in whom the first ASS occurred after CVT diagnosis (post-diagnosis ASS). Time to first post-diagnosis ASS for patients without presenting seizure is described in Figure 2. In 32 (34%) patients, post-diagnosis ASS occurred within the first 24 hours after diagnosis, and in 66 (71%) within the first 48 hours after diagnosis.

Table 1 compares the characteristics of patients with post-diagnosis ASS to patients without ASS. In multivariable analyses, predictors for post-diagnosis ASS were focal neurological deficit, ICH, cerebral edema/infarct only, superior sagittal sinus thrombosis, and cortical vein thrombosis (Table 2).

When calculating PPV and NPV for univariable predictors of post-diagnosis ASS, no variable achieved PPV over 25%. Highest predictive values were obtained for the variables focal neurological deficit and cortical vein thrombosis where PPV for post-diagnosis ASS were 17% and 22%, and NPV 97% and 92%, respectively.

Predictors of SE

Eighty (18% of those with ASS, 6% of the total cohort) patients developed SE in the acute phase and 70 (88%) of the incidences of SE occurred within 24 hours after diagnosis of CVT. In 37 patients, the first seizure was a SE. In multivariable logistic regression analysis, ICH (aOR 4.8, 95% CI 2.5-9.4), focal neurological deficits (aOR 4.7, 95% CI 2.2-10.1), and cerebral edema/infarct only (aOR 3.1, 95% CI 1.5-6.8) were predictors for SE.

Clinical outcome

Of the 1,281 patients, data of 1,106 (86%) could be included in the outcome analysis. The Adelaide cohort (n=97) and an additional 78 patients were excluded because they were followed-up for less than three months. Included patients were younger (median age at CVT diagnosis was 40 vs. 44, p=0.008), more often female (71% vs. 59%, p=0.003), more often had had baseline focal neurological deficits (59% vs. 39%, p<0.001), ICH (34% vs. 26%,

p=0.046), and were less frequently diagnosed with cancer (9% vs. 18%, p=0.001), compared to excluded patients.

The distribution of the mRS score at last follow-up in patients with and without ASS is shown in Figure 3. Median duration of follow up was 12 months (IQR 6-25) in the group with ASS and 12 months (IQR 6-25) in the group without ASS (p=0.876). Poor clinical outcome (mRS 2 to 6) was more common in patients with ASS compared to those without ASS (42% vs. 31%, p<0.001, Table 3). Mortality was not increased in patients with ASS (11% vs. 9%, p=0.345). After adjustment for prognostic factors, the presence of ASS was not associated with poor clinical outcome or mortality (Table 3). Clinical outcome at last follow-up did not differ between patients with pre-diagnosis ASS and patients with post-diagnosis ASS (data not shown). There was also no association between SE and clinical outcome (data not shown).

Discussion

In this large international observational study, we found that approximately one in three patients with CVT suffers from ASS. We confirmed that focal neurological deficits, ICH, superior sagittal sinus thrombosis, and cortical vein thrombosis are predictors for ASS.[2,4,5] In addition, we identified cerebral edema/infarction, sulcal SAH and female-specific risk factors as new independent predictors. ICH, focal neurological deficits and cerebral edema/infarction also predicted SE in the acute phase. No subgroup without pre-diagnosis seizures was found to have a risk of post-diagnosis ASS of more than 25%. Neither ASS nor SE were independently associated with clinical outcome.

The occurrence of ASS in our cohort essentially matches previous reports with approximately one third of the patients experiencing ASS.[1-3] Some previous reports used a period of 0-14

days for describing ASS. We used a limit of 7 days, in accordance with current recommendations.[15,16] To facilitate comparability with previous studies, we tested whether 14 days as the upper limit lead to different findings, which it did not (data available from Dryad [Tables e-2 and e-3 doi:10.5061/dryad.w6m905qm7]).

The strength of the predictors for ASS corresponds to the results of three previous CVT cohort studies.[2,4,5] However, in these studies, when both ICH and cerebral edema/infarction were present, patients were categorized separately in both categories, which potentially created an overlap between the two groups. We addressed this issue by separating patients with cerebral edema/infarction from patients with both ICH and cerebral edema/infarction, showing that cerebral edema/infarction alone also increases the risk of ASS after CVT. Accumulation of intracellular calcium, parenchymal structural damage or biochemical neuron damage as a cause of excitotoxic glutamate release secondary to hypoxia and ischemia have all been suggested as possible mechanisms for developing ASS after ischemic stroke.[19] In patients with ICH or SAH, hemoglobin degradation products (such as iron) or blood-borne factors (such as thrombin) may trigger epileptogenesis.[20] Not only the type of lesion, but also the location of the lesion seems to be important for development of ASS. Previous studies suggest that supratentorial lesions, and lesions anterior to the central sulcus are predictive of ASS.[1,5] We found similar associations in our cohort, but were unable to include lesion location to the multivariable analysis due to missing data. Compared to all CVT patients, women with CVT are relatively younger. Young age has been suggested a risk factor for developing post stroke epilepsy, which partly could explain why female-specific risk factors increased the risk of ASS.[21] In most animal models, estradiol increases excitability, whereas progesterone bears anticonvulsive properties.[22] However, there is no evidence that the use of exogenous sex hormones (i.e. oral contraceptives) increases the risk of seizures in young adults without epilepsy.[23]

SE occurred in 6% of all patients and in 18% of patients with ASS, which confirms previously reported frequencies of SE ranging from 0.5 to 11% among all patients and 1 to 22% among patients with ASS.[2,4,5,24] ICH, focal neurological deficits and cerebral edema/infarction were predictors for SE which resemble strong predictors of ASS.

In our study, one in ten patients who had not experienced a pre-diagnosis seizure, developed post-diagnosis ASS. This estimate is higher than in previous studies. In the Venoport study and International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), only 3% and 4% of patients without presenting seizures developed post-diagnosis ASS, respectively.[4,5] One explanation for the lower estimates in the ISCVT and Venoport studies could be that diagnostic delay has decreased over time. In our cohort, the median delay from symptom onset to diagnosis was four days, while this was seven days in the ISCVT. In the Venoport study, the median interval from symptom onset to diagnosis was not reported.

In absence of seizures, the European Stroke Organisation/European Academy of Neurology guidelines present no recommendation regarding prophylactic AED treatment, while the American Heart Association/American Stroke Association guidelines do not recommend routine use of AEDs in absence of seizures (Class III, level of evidence C).[9,11] Further, there are no studies that show that primary prophylactic treatment with AEDs reduces the risk of ASS or SE in CVT. A few studies did find that prophylaxis decreases the risk of ASS in patients with severe traumatic brain injury[25] and aneurysmal SAH.[26] In patients with spontaneous ICH and arterial ischemic stroke, primary prophylactic use of AEDs is not recommended.[27,28] There is some evidence that AEDs reduce the risk of seizures in patients with spontaneous ICH in the acute phase,[29] but the use of prophylactic AEDs, especially phenytoin, has also been associated with a worse clinical outcome.[30,31] In our study, we could not identify a specific subgroup of patients without pre-diagnosis seizures that would be eligible for primary prophylactic AEDs, i.e. that had such a high risk to develop post-

diagnosis ASS that the potential benefit from an AED could outweigh the risk of side effects. Moreover, the data from our study indicate that, if one would consider prescribing AEDs in patients with CVT, it needs to be administered as soon as possible after the diagnosis, since most patients developed post-diagnosis seizures, including SE, within 48 hours after diagnosis. In our study, choices of ASS treatments reflected use of intravenously available AEDs of which concentrations can easily be measured in serum guiding treatments.

Although one previous study reported an association between ASS and increased early mortality,[5] we found no association between ASS nor SE and clinical outcome after adjustment for other prognostic variables. A possible explanation why other studies found an association is that these may not have properly adjusted for confounders. Some of the predictors of ASS, such as focal deficits and ICH, also increase the risk of poor outcome. Further, we found no difference between patients with pre-diagnosis ASS and patients with post-diagnosis ASS regarding clinical outcome, suggestive of comparable severity of epileptic activity between the two groups.

Several limitations of our study warrant comment. First, the main aim of this study, to identify predictors for ASS, was not a pre-defined question when cases were enrolled in the cohort and thus the study lacks predefinition of variables. Although all patients are consecutive, some of the data were collected retrospectively. Second, because most centers in the CVT consortium function as a tertiary referral center for CVT, we may have an overrepresentation of severe cases, and thus of seizures, in our cohort. Third, due to the observational design of the study and limited numbers of patients with ASS not receiving an AED, we were not able to assess treatment effects of AEDs. The assessment of AED treatment efficacy would require taking into account multiple potential confounding factors such as exact dosages, AED serum concentrations, treatment duration, and justifies a separate study to be answered properly. Finally, despite not being limited to clinical diagnosis alone, most seizures were diagnosed

clinically and in lack of routine EEG monitoring, non-convulsive seizures could not be systematically investigated.

To summarize, our study shows that ASS occur in approximately one third of all patients with CVT. ICH, cerebral edema/infarction, cortical vein thrombosis, superior sagittal thrombosis, focal neurological deficit, sulcal SAH and female-specific risk factors were all predictors for ASS in CVT. Post-diagnosis ASS were common, but in absence of pre-diagnosis ASS, no risk factor sufficiently predicted the development of post-diagnosis seizures to justify primary prophylactic AED treatment. Predictors for development of SE in the acute phase resembled strong predictors for ASS and were ICH, focal neurological deficits and cerebral edema/infarction. Finally, we found no influence of ASS on functional outcome after three or more months in CVT patients.

Acknowledgments

Appendix 1: Authors

Name	Location	Contributions
Erik Lindgren, MD	Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg and Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden	Designed and conceptualized the study; analyzed the data; major role in the acquisition of data; drafted and reviewed the manuscript for intellectual content
Suzanne M Silvis, MD	Department of Neurology, Amsterdam UMC, University of Amsterdam, The Netherlands	Designed and conceptualized the study; analyzed the data; major role in the acquisition of data; drafted and reviewed the manuscript for intellectual content
Sini Hiltunen, MD, PhD	Department of Neurology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland	Major role in the acquisition of data; revised the manuscript for intellectual content
Mirjam R	Department of Neurology, Inselspital, Bern	Major role in the

Heldner, MD, MSc	University Hospital and University of Bern, Bern, Switzerland	acquisition of data; revised the manuscript for intellectual content
Fabiola Serrano, MD	National Institute of Neurology and Neurosurgery Manuel Velasco Suarez, Mexico-City, Mexico	Major role in the acquisition of data; revised the manuscript for intellectual content
M de Scisco, MD	Department of Neurology, Royal Adelaide, Hospitals and Department of Medicine, University of Adelaide, Adelaide, SA, Australia	Major role in the acquisition of data; revised the manuscript for intellectual content
Johan Zelano, MD, PhD	Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg and Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden	Designed and conceptualized the study; interpreted data; revised the manuscript for intellectual content
Susanna M. Zuurbier, MD, PhD	Amsterdam University Medical Center, Amsterdam, The Netherlands	Major role in the acquisition of data; revised the manuscript for intellectual content

Mayte Sánchez van Kammen, MD	Department of Neurology, Amsterdam UMC, University of Amsterdam, The Netherlands	Major role in the acquisition of data; revised the manuscript for intellectual content
Maryam Mansour, MD	Sina Hospital, Hamadan University of Medical Science, Hamadan, Iran	Major role in the acquisition of data; revised the manuscript for intellectual content
Diana Aguiar de Sousa, MD, MSc, PhD	Department of Neurosciences and Mental Health, Hospital de Santa Maria/CHULN; University of Lisbon, Lisbon, Portugal	Major role in the acquisition of data; revised the manuscript for intellectual content
Sara Penas, MD	Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal	Major role in the acquisition of data; revised the manuscript for intellectual content
Saleem Al-Asady	Faculty of Biology, Medicine and Health, Manchester Medical School, University of Manchester, Manchester, United Kingdom	Major role in the acquisition of data; revised the manuscript for intellectual content

Esme Ekizoglu, MD	Department of Neurology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey	Major role in the acquisition of data; revised the manuscript for intellectual content
Petra Redfors, MD, PhD	Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg and Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden	Designed and conceptualized the study; interpreted data; revised the manuscript for intellectual content
Awet Ahmed, MD	Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg and Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden	Major role in the acquisition of data; revised the manuscript for intellectual content
Nilufer Yesilot, MD	Department of Neurology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey	Major role in the acquisition of data; revised the manuscript for intellectual content
Masoud Ghiasian, MD, PhD	Sina Hospital, Hamadan University of Medical Science, Hamadan, Iran	Major role in the acquisition of data; revised the manuscript for

		intellectual content
Miguel A Barboza, MD, PhD	Neurosciences Department, Hospital Dr. R.A. Calderón Guardia, CCSS, San José, Costa Rica	Major role in the acquisition of data; revised the manuscript for intellectual content
Valencia Arnao, MD, PhD	Department of Biomedicine, Neuroscience and Advanced Diagnostics (Bi.N.D), University of Palermo, Palermo, Italy	Major role in the acquisition of data; revised the manuscript for intellectual content
Aridon P, MD, PhD	Department of Biomedicine, Neuroscience and Advanced Diagnostics (Bi.N.D), University of Palermo, Palermo, Italy	Interpreted the data; revised the manuscript for intellectual content
Martin NM Punter, MD, PhD	Manchester Centre for Clinical Neurosciences, Salford Royal NHS Foundation Trust, Manchester, United Kingdom	Major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
José M Ferro, MD, PhD	Department of Neurosciences and Mental Health, Hospital de Santa Maria/CHULN; University of Lisbon, Lisbon, Portugal	Major role in the acquisition of data; interpreted the data; revised the

		manuscript for intellectual content
Timothy Kleinig, MD, PhD	Department of Neurology, Royal Adelaide, Hospitals and Department of Medicine, University of Adelaide, Adelaide, SA, Australia	Major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
Antonio Arauz, MD, PhD	National Institute of Neurology and Neurosurgery Manuel Velasco Suarez, Mexico-City, Mexico	Major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
Turgut Tatlisumak, MD, PhD	Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg and Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden. Department of Neurology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland	Guarantor of the study; designed and conceptualized the study; major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
Marcel Arnold, MD	Department of Neurology, Inselspital, Bern University Hospital and University of Bern,	Interpreted the data; major role in the

	Bern, Switzerland	acquisition of data; revised the manuscript for intellectual content
Jukka Putaala, MD, PhD	Department of Neurology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland	Interpreted the data; major role in the acquisition of data; revised the manuscript for intellectual content
Jonathan M Coutinho, MD, PhD	Department of Neurology, Amsterdam UMC, University of Amsterdam, The Netherlands	Designed and conceptualized the study; major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
Katarina Jood, MD, PhD	Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg and Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden	Designed and conceptualized the study; major role in the acquisition of data; interpreted the data; revised the manuscript for

		intellectual content

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Figure 1: Flowchart of patient selection

Patients in whom the first seizure occurred prior to diagnosis of CVT were categorized as pre-diagnosis ASS, while patients in whom the first seizure occurred after diagnosis of CVT were categorized as post-diagnosis ASS.
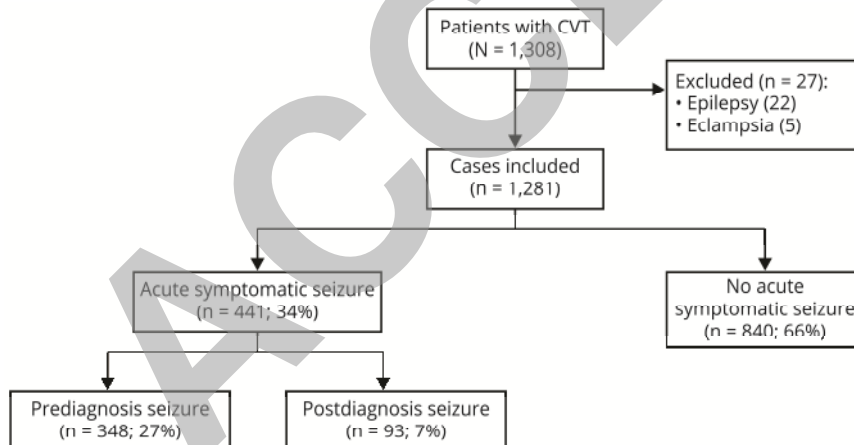
Figure 2: Time to first post-diagnosis acute symptomatic seizure

Number of patients (n=93) experiencing a first post-diagnosis acute symptomatic seizure, fractionated per day after diagnosis of cerebral venous thrombosis.
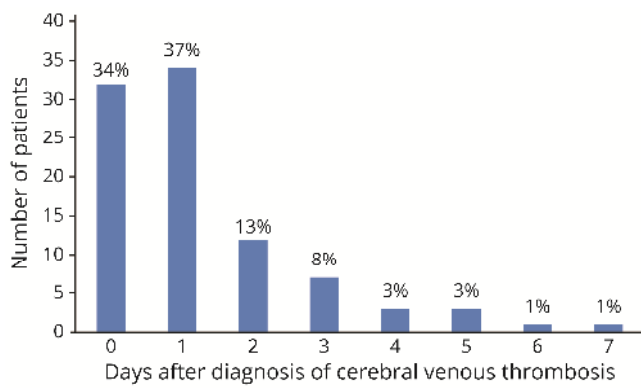

Figure 3: Distribution of mRS scores at last follow-up for patients with and without acute symptomatic seizures

Abbreviations: mRS = modified Rankin Scale; ASS = acute symptomatic seizures
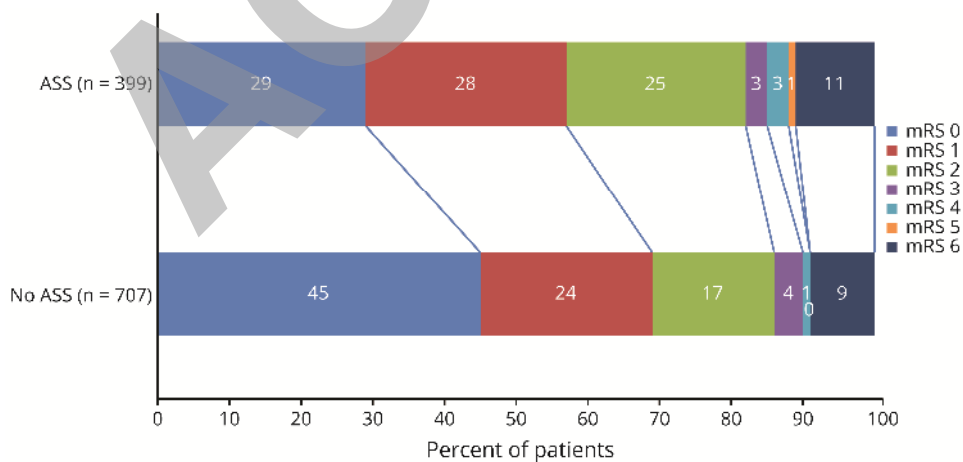
Table 1: Baseline characteristics and treatment

	No acute symptomatic seizures n=840 (ref)	Acute symptomatic seizures n=441	P-value[a]	Solely post-diagnosis seizures n=93	P-value[a]
Clinical characteristics					
Women, n/N (%)	559/840 (67%)	324/441 (74%)	0.011	77/93 (83%)	0.001
Age in years - median (IQR)[b]	41 (30-53)	40 (29-52)	0.280	36 (26-47)	0.015
Acute symptom onset <48 hours, n/N (%)	240/808 (30%)	167/431 (39%)	0.001	31/91 (34%)	0.400
Focal neurological deficits, n/N (%)	385/835 (46%)	328/441 (74%)	<0.001	79/93 (85%)	<0.001
Coma (GCS<9), n/N (%)	29/834 (4%)	41/439 (9%)	<0.001	5/93 (5%)	0.376
Risk factors, n/N (%)					
Oral contraceptive use[c]	225/554 (41%)	139/322 (43%)	0.477	36/76 (47%)	0.267
Pregnancy, puerperium[c]	56/559 (10%)	49/324 (15%)	0.031	11/77 (14%)	0.239
Hormone replacement therapy[c]	22/559 (4%)	15/323 (5%)	0.606	1/77 (1%)	0.342
Any female-specific risk factor[c]	308/557 (55%)	200/324 (62%)	0.066	46/77 (60%)	0.541
Cancer	88/836 (11%)	43/440 (10%)	0.699	10/93 (11%)	0.861
Infection	101/834 (12%)	50/441 (11%)	0.716	13/93 (14%)	0.617
Imaging characteristics, n/N (%)					
Any parenchymal lesion	328/839 (39%)	337/441 (76%)	<0.001	70/93 (75%)	<0.001
Intracerebral hemorrhage	187/840 (22%)	228/441 (52%)	<0.001	43/93 (46%)	<0.001
Cerebral edema/infarct only	128/840 (15%)	101/441 (23%)	0.001	24/93 (26%)	0.012
Lesion location[d]					
Supratentorial	264/668 (40%)	288/378 (76%)	<0.001	65/86 (76%)	<0.001
Cortical lesion	171/658 (26%)	210/351 (60%)	<0.001	52/83 (63%)	<0.001

Subcortical lesion	96/657 (15%)	67/351 (19%)	0.073	13/82 (16%)	0.742
Sulcal subarachnoid hemorrhage	59/839 (7%)	73/441 (17%)	<0.001	11/93 (12%)	0.099
Subdural hematoma	19/838 (2%)	13/441 (3%)	0.457	0/93 (0%)	0.245
Superior sagittal sinus thrombosis	364/836 (44%)	284/441 (64%)	<0.001	67/93 (73%)	<0.001
Lateral sinus thrombosis	607/838 (72%)	256/440 (58%)	<0.001	60/93 (65%)	0.115
Cortical vein thrombosis	104/838 (12%)	139/441 (32%)	<0.001	30/93 (32%)	<0.001
Straight sinus thrombosis	159/837 (19%)	47/441 (11%)	<0.001	10/93 (11%)	0.064
Treatment and admission					
Hospital stay in days (median, IQR)	9 (6-14)	12 (8-18)	<0.001	14 (9-19)	<0.001
Intensive Care Unit admission, n/N (%)	86/756 (11%)	138/439 (31%)	<0.001	27/93 (29%)	<0.001
Anticoagulation, n/N (%)	761/837 (91%)	422/441 (96%)	0.002	87/93 (94%)	0.562
Decompressive hemicraniectomy, n/N (%)	31/838 (4%)	24/441 (5%)	0.149	4/93 (4%)	0.772
Endovascular treatment, n/N (%)	38/838 (5%)	25/441 (6%)	0.415	4/93 (4%)	0.772
Type of antiepileptic drug treatment					
among patients with ASS, n/N (%)					
Phenytoin		182/432 (42)			
Levetiracetam		150/433 (35)			
Valproic acid		108/432 (25)			
Carbamazepine		52/433 (12)			
Other		30/433 (7)			
Combination		103/435 (24)			
No AED treatment		26/433 (6)			

Abbreviations: IQR = interquartile range; GCS = Glasgow coma scale. [a] Compared to no acute symptomatic seizures; [b] No missing data; [c] Percentage of women; [d] Data are missing from two centers, n=317;

Table 2: Predictors for acute symptomatic seizures and post-diagnosis seizures

	Acute symptomatic seizures, adjusted OR, (95% CI)	Post-diagnosis seizures, adjusted OR, (95% CI)
Age	1.0 (1.0-1.0)[a]	1.0 (1.0-1.0)[b]
Female sex	1.0 (0.7-1.4)	1.8 (1.0-3.3)[c]
Intracerebral hemorrhage	4.1 (3.0-5.5)	2.8 (1.6-4.8)
Cerebral edema/infarct only	2.8 (2.0-4.0)	2.3 (1.3-4.4)
Cortical vein thrombosis	2.1 (1.5-2.9)	2.5 (1.5-4.2)
Superior sagittal thrombosis	2.0 (1.5-2.6)	2.2 (1.3-3.7)
Focal neurological deficit	1.9 (1.4-2.6)	4.1 (2.2-7.5)
Sulcal subarachnoid hemorrhage	1.6 (1.1-2.5)	1.0 (0.5-2.1)
Female-specific risk factors	1.5 (1.1-2.1)	N/A

OR = odds ratio; CI = confidence interval. [a]p=0.512; [b]p=0.192; [c]p=0.059

Table 3: Clinical outcome

	Acute symptomatic seizures, n=399	No acute symptomatic seizures, n=707	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)
mRS 2-6	169/399 (42%)	218/707 (31%)	1.6 (1.3-2.1)	1.1 (0.8-1.4)
Mortality	44/399 (11%)	65/707 (9%)	1.2 (0.8-1.8)	0.8 (0.5-1.3)

OR = odds ratio, CI = confidence interval, mRS = modified Rankin Scale
[a] Adjusted for age, female sex, focal neurological deficits, coma, infection, intracerebral hemorrhage, subdural hematoma, sulcal subarachnoid hemorrhage and cancer

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