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ORIGINAL ARTICLE

Severe Cerebral Venous and Sinus Thrombosis: Clinical Course, Imaging Correlates, and Prognosis

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Abstract

Background Severe cerebral venous-sinus thrombosis (CVT) is a rare disease, and its clinical course, imaging correlates, as well as long-term prognosis have not yet been investigated systematically.

Methods Multicenter retrospective study. Inclusion criteria were CVT, Glasgow coma scale ≤ 9, and treatment in the intensive care unit. Primary outcome was death or dependency, assessed by a modified Rankin Score (mRS) >2 at last follow-up.

Results 114 patients were included. At last follow-up (median 2.5 years), 38 patients (33.3 %) showed no or minor residual symptoms (mRS = 0 or 1), 12 (10.5 %) had a mild (mRS = 2), 13 (11.4 %) a moderate (mRS = 3), 12 (10.5 %) a severe disability (mRS = 4 or 5), and 39 (34.2 %) had died. In bivariate analysis, predictors of poor outcome were any signs of mass effect on imaging, clinical deterioration after admission, and age. In contrast, clinical symptoms on admission and parenchymal lesions per se, such as edema, infarction, or hemorrhage were not predictive. Multivariate predictors of poor outcome were an increase in National Institutes of Health Stroke Scale ≥ 3

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after admission [odds ratio (OR) 6.7], bilateral motor signs in the further course (OR 9.2), and midline shift (OR 5.1). *Conclusion* The outcome of severe CVT is almost equally divided between severe impairment or death and survival with no or only mild handicap. Specifically, space-occupying mass effect and associated neurologic deterioration seem to determine a poor outcome. Therefore, early detection and treatment of mass effect should be the focus of critical care.

Keywords Cerebral venous thrombosis · Stroke · Prognosis · Neurocritical care · Intensive care

Introduction

Thrombosis of the dural sinus and/or cerebral veins (CVT) is an infrequent cause of stroke, representing approximately 1 % of all strokes and preferably affecting young individuals [1, 2]. The International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) is the largest prospective study on outcome after CVT and showed that approximately 75 % of patients with CVT have a favorable outcome [3]. However, at least 13 % of all patients with CVT die or remain severely handicapped [3–7]. Several risk factors for such poor outcome have been identified, including coma, intracerebral hemorrhage, and thrombosis of the deep venous system [3]. Patients with these risk factors are often regarded as a subpopulation eligible for escalation of treatment beyond anticoagulation, such as endovascular thrombolysis/thrombectomy or decompressive hemicraniectomy, which have been reported anecdotically or in case series [8–17]. However, this rare subtype of CVT with severe clinical course has never been studied systematically with regard to clinical course, imaging correlates, prognostic factors, and long-term outcome.

Methods

Organization of Study and Patients

We performed a retrospective, national multicenter study including patients with CVT confirmed by CT venography, MR venography, or conventional angiography, with a Glasgow Coma Scale score (GCS) ≤ 9 on admission or during the clinical course, who were treated in an intensive care unit (ICU).

Patients were identified by ICU documentation and/or clinical coding systems for the time period between 1996 and 2011. Patients were followed-up between June 2012 and July 2013. Participating centers submitted a case report form (CRF) for each included patient, which was sent to the coordinating center in Cologne. All participating centers were tertiary care hospitals. Ethics approval was obtained from the local ethics committees of all centers.

Demographic and Clinical Data, Risk Factors, Imaging, and Treatment

We recorded the following information according to the protocol of the ICVST study [3]: demographic data, risk factors for CVT, time of symptom onset, of hospital admission and of imaging confirming the diagnosis; clinical symptoms on admission and during clinical course; mode of onset (acute: <2 days, subacute: 2–30 days, chronic: >30 days); GCS and National Institute of Health Stroke Scale score (NIHSS) on admission and at discharge; lowest GCS and highest NIHSS during the clinical course; imaging methods used and timepoint of imaging; and prespecified treatment elements were systematically recorded. If patients were intubated and sedated for >2 days, the minimal GCS was recorded as 3, if the intubation period was shorter, the lowest GCS before or after intubation was recorded as minimal GCS.

Radiologic Analysis

Copies of all available cerebral images acquired during hospitalization were analyzed by two neuroradiologists blinded for any clinical data. The images were evaluated for: location of thrombus (superior sagittal sinus, lateral sinus right/left, straight sinus, deep venous system, confluence of sinuses, sigmoid sinus right/left, jugular vein right/left); presence and location of parenchymal lesions (hemorrhage, infarction, edema), hydrocephalus, and signs and extent of space-occupying mass effect (herniation, midline shift, compression of ventricles, sulcal effacement, obliteration of basal cisterns). To grade the extent of parenchymal lesions and mass effect, each variable was subdivided and ranked ordinally ranging from absence of the variable to a pronounced bilateral or even supra- and infratentorial affection (see Table 2). Individual longitudinal imaging data were transferred to individual cross-sectional data, and maximal extent of lesions, mass effect, and sinus affection were used for statistical analysis.

Follow-Up and Outcome

The follow-up data included disability and death assessed by the modified Rankin Scale (mRS), and any complications including recurrent CVT. The mRS between 3 and 9 months after hospital stay was assessed either during follow-up visits or from patient records. For long-term outcome, the mRS was assessed at the time of the study

between June 2012 and July 2013 by a full checkup of the patients at their corresponding hospital or, if that was not feasible, by telephone interview of either the patient, a relative, or a caregiver. If patients were lost to follow-up, the mRS at discharge was regarded as last follow-up. Poor outcome was defined as death or dependence (mRS >2) at last follow-up, good outcome as no or only mild disability (mRS 0–2).

Statistical Analysis

Demographic, clinical, and imaging data as well as CVT risk factors were evaluated statistically by means of bivariate analysis using the Fisher's exact test for categorical variables and the Kruskal–Wallis test for continuous variables. Comparison of the extent of parenchymal lesions and of mass effect between the outcome groups as well as possible associations between clinical deterioration and imaging variables were calculated using the Fisher's exact test. A p value < 0.05 was considered statistically significant, even though not corrected for multiple testing. All reported p values are two-sided. Variables significantly associated with poor outcome were included in a multivariate logistic regression model (with backward selection). Odds ratios (ORs) and 95 % confidence intervals (CI) were calculated for the retained variables.

Imaging data were available for 76 patients only, thus all results based on imaging parameters refer to this cohort of patients. Demographic and clinical variables and CVT risk factors are related to the entire population (114 patients). The multivariable logistic regression model was based on the 76 cases with imaging results. Data were analyzed with SPSS 22.0 for Windows.

Results

Patient Characteristics

114 patients from ten centers were included in the study. Mean age was 44.7 years (range 13–81), and 82 patients (72 %) were female. Median delay from onset of symptoms to hospital admission was 1 day (range 0–33), to diagnosis 2 days (range 0–35), and to ICU admission 3 days (0–36). The diagnosis of CVT was established by MRI/MR venography in 54 patients (47 %), by CT venography in 62 (54 %), by intra-arterial angiography in 14 patients (12 %), and by multiple imaging methods in 16 patients (14 %). The mode of onset was acute in 66 patients (58 %), subacute in 47 patients (41 %), and chronic in 1 patient (0.9 %). On hospital admission, median GCS was 10 (range 3–15), median NIHSS was 9 (range 0–29), and 40 patients (35.4 %) were comatose. Reasons for coma on hospital admission were cerebral lesions in most cases (often combined), i.e., edema (18; 45 %), intracerebral hemorrhage (ICH) and/or infarction (18; 45 %), often associated with epileptic seizures (18; 45 %), whereas sepsis (3; 7.5 %) or cardiac problems (1; 2.5 %) were less frequently the reason for coma on admission.

Minimal median GCS score during the clinical course was 3 (range 3–9) reached after a mean of 5.3 days, and maximal median NIHSS was 25 (range 4–32) reached after a mean of 5.7 days. Forty-six patients (41.8 %) experienced a secondary neurologic deterioration (ΔNIHSS $\geq$3 points) during clinical course outlasting discharge. Eighty percent of patients were mechanically ventilated with a mean duration of 9.6 days. Mean duration of ICU stay was 12.6 days, and mean duration of hospital stay was 19.7 days.

Clinical symptoms on admission and during the clinical course are shown in Table 1. We noted that a high number of patients showed focal neurologic deficits, which increased during the clinical course.

Complete imaging datasets for detailed radiologic analysis were available from 76 patients. A total of 427 scans were analyzed with a median of 5 serial scans per patient (range 1–14). Reasons for missing imaging data were incomplete datasets ($n = 13$) or non-availability of imaging data in several centers ($n = 25$).

Table 2 shows the incidences of parenchymal lesions, of mass effect as well as the affected sinuses/veins during the clinical course. All patients exhibited one or more parenchymal lesions such as edema, infarction, or hemorrhage. A substantial number of patients showed space-occupying mass effect on imaging, ranging from only local supratentorial signs to severe supra- and infratentorial signs of mass effect. The deep venous system was affected in 28 patients (36.8 %). The sum of affected sinuses/veins is higher than 100 % because more than one sinus/vein could be affected in individual patients.

A systematic diagnostic workup of thrombophilia was performed in 72.8 % of the patients. All risk factors for CVT are listed in detail in the appendix. Eighty-two patients (71.9 %) had more than one known risk factor.

In the acute phase, most patients (106, 93 %) were anticoagulated, 95 (83.3 %) with intravenous heparin, 9 (7.9 %) with low molecular weight heparin, and 2 (1.8 %) with lepirudin in therapeutic dosages. Mean delay between symptom onset and start of anticoagulation was 4.8 days (median 2; range 0–34). Reasons to withhold anticoagulation throughout the clinical course (8 patients) were intracerebral hemorrhage (3), sepsis (1), surgery (1), or were not stated (3).

Median PTT level in patients treated with i.v. heparin was 70 s, with a median lower level of 60 s (range 40–80) and a median upper level of 75 s (range 45–120).

Table 1 Clinical features on admission and during clinical course

	Symptoms on admission		Symptoms during clinical course	
	No. of cases	%	No. of cases	%
Headache	85	74.6	71	62.3
Visual loss	14	12.3	14	12.3
Diplopia	5	4.4	9	7.9
Aphasia	30	26.3	34	29.8
Altered mental status	54	47.4	62	54.4
Any paresis	55	48.2	74	64.9
Left	33	28.9	43	37.7
Right	26	22.8	45	39.5
Bilateral motor signs	7	6.1	25	21.9
Brain stem areflexia	0	0	6	5.3
Any seizure	45	39.5	34	29.8
Focal	21	18.4	17	14.9
With generalization	40	35.1	27	23.7
Status epilepticus	15	13.2	10	8.8
Sensory symptoms	19	16.7	22	19.3
Other focal cortical sign	13	11.4	16	14.0

In the 69 patients with serial imaging and anticoagulation, we found an increase of hemorrhage in 21 patients (30.4 %) and a new hemorrhage in 8 patients (11.6 %). Interestingly, such an increase of hemorrhage or new bleeding occurred in 6 of these 29 patients after start of i.v. heparin but before the goal level of anticoagulation was reached. In contrast, 3 (60 %) of 5 patients with serial imaging but without anticoagulation showed an increase of hemorrhage.

Clinical signs of intracranial hypertension were documented in 40 % of patients and increased ICP was treated in 49.1 %. Specific treatments of increased ICP were osmotherapy (46; 40.4 %), extraventricular drainage/shunt (24; 21.1 %), diuretics (20; 17.5 %), steroids (17; 14.9 %), barbiturates (10; 8.8 %), hypothermia (10; 8.8 %), hyperventilation (5; 4.4 %), acetazolamide (3; 2.6 %), and lumbar drainage (2; 1.8 %).

Twenty-two patients (19.3 %) were treated with local endovascular therapy: 7 with local thrombolysis, 5 with mechanical thrombectomy, and 10 with a combination of both. Twenty-three patients (20.2 %) underwent decompressive craniectomy after a mean of 10 days from symptom onset.

Outcome

Information on outcome at discharge was available for all patients and the follow-up status was reported for 98.2 % of the patients (Fig. 1). Outcome data at 3–9 months was available for 98 patients (86 %). For long-term follow-up, the mRS was obtained in 91 patients (79.8 %) at the time of the study. In 6 patients (5.3 %), the mRS at 12 months or later was obtained from the patients' records and regarded as the last follow-up, in 15 cases (13.2 %) the mRS after 3–9 months was the last follow-up. Two patients (1.8 %) were lost to follow-up so that the mRS at discharge was regarded as last follow-up. Mean time of follow-up was 3.9 years (median 2.5). Twenty-nine patients (25.4 %) died during hospital treatment. In 8 of the 39 patients who had died in the last follow-up, death was not caused by CVT.

Events occurring during follow-up were epileptic seizures (14 patients, 14.3 %), severe headache (6, 5.3 %), visual loss (6, 5.3 %), limb or pelvic venous thrombosis (5, 4.4 %), or pulmonary embolism (3, 2.6 %); no symptomatic new CVT was reported.

Prognostic Factors

Clinical variables predictive of poor outcome in the bivariate analysis are shown in Table 3. The outcome was found to be independent from clinical symptoms and scores (NIHSS, GCS) on admission, from all risk factors for CVT, from the mode of symptom onset, and from the anatomic location of the affected sinuses/veins. Particularly, signs of neurologic deterioration during the clinical course were associated with dependency or death at follow-up. Table 4 shows prognostic imaging variables.

All variables for mass effect were highly predictive for dependence or death at follow-up while the presence of a

Table 2 Imaging features: parenchymal lesions, mass effect, and affected sinus/vein

	No. of cases	%
Edema	71	93.4
Unilateral supratentorial	39	51.3
Bilateral supratentorial	31	40.8
Supra- and infratentorial	1	1.3
Edema of thalamus and basal ganglia	18	23.7
Unilateral	2	2.6
Bilateral	16	21.1
Infarction	47	61.8
Unilateral supratentorial	31	40.8
Bilateral	16	21.1
Supra- and infratentorial	0	0
Hemorrhage	61	80.3
Unilateral supratentorial	41	54.0
Bilateral supratentorial	18	23.7
Supra- and infratentorial	2	2.6
Hydrocephalus	30	39.5
Sulcal effacement	63	82.9
Unilateral supratentorial focal	15	19.7
Bilateral supratentorial focal	2	2.6
Unihemispheric total	13	17.1
Bihemispheric total	29	38.2
Supra- and infratentorial	4	5.3
Ventricle compression	46	60.5
Focal compression	15	19.7
Unilateral compression supratentorial	18	23.7
Bilateral compression supratentorial	11	14.5
Supra- and infratentorial	2	2.6
Obliteration of basal cisterns	35	46.1
Midline shift	34	44.7
<1 cm	21	27.6
>1 cm	13	17.1
Herniation	26	34.2
Supratentorial	4	5.3
Transtentorial	7	9.2
Supra- and transtentorial	6	7.9
Supra-/transtentorial and infratentorial	9	11.8
Occluded sinus/vein		
Superior sagittal sinus	47	61.8
Lateral sinus, left	28	36.8
Lateral sinus, right	18	23.7
Straight sinus	32	42.1
Deep venous system	28	36.8
Confluence of sinuses	42	55.3
Sigmoid sinus left	14	18.4
Sigmoid sinus right	9	11.8
Jugular vein left	14	18.4
Jugular vein right	8	10.5

	3-9 months		Long-term follow-up	
	n = 98		n = 114	
	No. of cases	%	No. of cases	%
mRS				
0-2	36	36.7	50	43.9
3-6	62	63.3	64	56.1

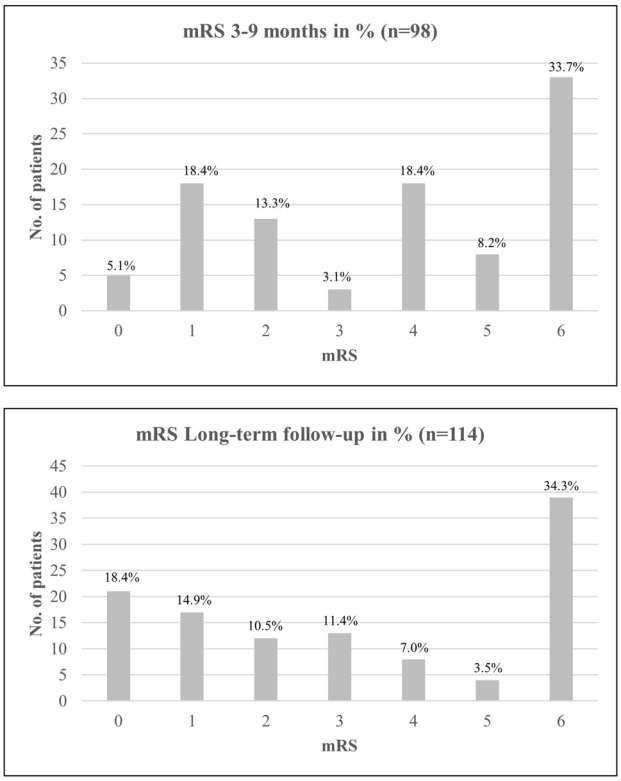

Fig. 1 Outcome of patients

parenchymal lesion per se was not. Hemorrhage ($p = 0.084$) and infarction ($p = 0.062$) tend to occur more frequently in the patients with eventually poor outcome, but did not reach statistical significance.

When the extent of parenchymal lesions and mass effect variables (as shown in Table 2) were compared between the outcome groups, all variables of mass effect were significantly associated with poor outcome, while edema ($p = 0.29$), infarction ($p = 0.12$), and hemorrhage ($p = 0.07$) were not (Table 4). We found a difference in outcome in favor of the patients with edema of thalamus/basal ganglia ($p = 0.007$).

Neurologic deterioration, i.e., increase of NIHSS ≥ 3 points was found to be associated with mass effect ($p < 0.001$ for all variables of mass effect) and with infarction ($p = 0.016$), while hemorrhage ($p = 0.079$) and edema ($p = 0.392$) failed to be significant. The same association with mass effect and infarction was found for a decline of GCS ≥ 3 points. For further comparison of

Table 3 Prognostic factors, bivariate analysis: clinical variables

Variables	mRS 0–2 ($n = 50$) No. (%)	mRS 3–6 ($n = 64$) No. (%)	p value
Secondary clinical deterioration			
NIHSS ≥3 points	5 (10.0)	41 (64.1)	<0.001
GCS ≥3 points	0	32 (50)	<0.001
Bilateral motor signs during clinical course	4 (8.0)	21 (32.8)	0.001
Status epilepticus during clinical course	1 (2.0)	9 (14.1)	0.041
Minimal GCS during clinical course (mean)	6.0	4.0	<0.001
Maximal NIHSS during clinical course (mean)	18.1	23.4	<0.001
Age (mean)	40.1	48.4	0.019

Table 4 Prognostic factors, bivariate analysis: imaging variables

Variable	mRS 0–2 ($n = 39$) No. (%)	mRS 3–6 ($n = 37$) No. (%)	p value
Any midline shift	9 (23.1)	25 (67.6)	<0.001
Any signs of herniation	4 (10.3)	22 (59.5)	<0.001
Any sulcal effacement	27 (69.2)	36 (97.3)	0.001
Obliteration of basal cisterns	11 (28.2)	24 (64.9)	0.003
Any ventricle compression	17 (43.6)	29 (78.4)	0.002
Any infarction	20 (51.3)	27 (73.0)	n.s.
Any hemorrhage	28 (71.8)	33 (89.2)	n.s.
Hydrocephalus	11 (28.2)	19 (51.4)	n.s.
Any edema	35 (89.7)	36 (97.3)	n.s.
Edema thalamus/basal ganglia	13 (33.3)	5 (13.5)	n.s.
Extent of herniation			<0.001
Extent of sulcal effacement			0.001
Extent of midline shift			<0.001
Extent of compression of ventricles			0.002
Extent of edema			n.s.
Extent of hemorrhage			n.s.
Extent of infarction			n.s.

For definition of extent of mass effect and parenchymal lesions, see also Table 2

imaging data between patients with and without neurological deterioration see appendix.

In multivariate analysis, only neurologic deterioration with an increase of the NIHSS score of ≥3 (OR 6.7, 95 % CI 1.6–28.0), midline shift (OR 5.1, 95 % CI 1.2–21.5), and bilateral motor sign (OR 9.2, 95 % CI 1.3–64.2) were independently associated with dependency or death.

Discussion

The main objective of this study was to investigate the outcome after severe CVT requiring ICU treatment and to identify parameters associated with outcome as possible prognostic factors. In accordance with the severity of symptoms in our patient series, the outcome results were poorer than reported in the ISCVT study on CVT cases in general: more than half of the patients were dead or dependent at long-term follow-up [3]. Most importantly, however, the other half of patients in our study survived with no or only mild deficits including one-third of patients with an excellent outcome. As the most robust parameters were associated with poor outcome, we identified neurologic deterioration and signs of mass effect on imaging. In contrast, clinical symptoms on admission and parenchymal lesions per se, i.e., edema, infarction, or hemorrhage, were not found to be predictive of a poor outcome in our cohort. Results from the ISCVT study group have also shown worsening of previous or de novo focal deficits to increase the risk of poor outcome in patients with CVT [18], but,

opposed to our results, hemorrhage was identified as an independent predictor of poor outcome in ISCVT [3, 18]. The different finding in our study might be explained by the fact that the vast majority of our patients (80.3 %) had a hemorrhage compared to only 39 % in the ISCVT study [3], which might have diminished the discriminative power of this variable concerning outcome. The same is true for edema formation and infarction. The fact that also the extent of hemorrhage and infarction did not reach statistical significance for prediction of poor outcome might be due to the low number of patients with multilocular hemorrhage or infarction. Since poor outcome seems to be determined by the space-occupying effect of parenchymal lesions rather than by the presence of parenchymal lesions itself, we suggest that the prediction of outcome and the decision to escalate or, worse, to limit therapy should not be based on the presence of parenchymal lesions alone but that visible mass effect should be emphasized as the leading indicator of deterioration determining the outcome. Thrombosis of the deep cerebral venous system was not found to be independently predictive of poor outcome in our study. To the contrary, presence and extent of edema in thalamus/basal ganglia, which typically reflects thrombosis of the deep cerebral venous system was more often associated with favorable outcome. This finding is in concordance with the results of Pfefferkorn et al. [19], who showed that the outcome of patients with affection of the deep cerebral venous system is good or even excellent, unless patients deteriorate clinically with progressive coma. On the other hand, the prospective ISCVT study identified thrombosis of the deep cerebral venous system as a predictor of poor outcome [3]. This discrepancy might well be explained by the highly selected patients with a more severe and comparatively acute clinical course in our study.

Based on our results, we suggest that all patients with severe CVT should be closely monitored for developing signs of a mass effect, ideally in a specialized neurointensive care unit since early detection and treatment could improve outcome. Treatment of patients beyond anticoagulation was heterogenous in our patients and our study was not designed to reliably assess specific treatment effects. Therefore, therapeutic recommendations cannot be derived from our study. With regard to treatment of space-occupying mass effect, we would like to highlight previous studies on the effect of decompressive surgery in CVT patients with mass effect [12–16]. Ferro et al. [12] showed that outcome after decompressive surgery can be surprisingly good even though almost half of these patients showed clinical signs of advanced herniation with uni- or even bilaterally dilated pupils before surgery. In four retrospective case series with a satisfactory outcome, the median preoperative midline shift was 9 mm or more [13–16]. In most cases, decompressive surgery was considered and applied only relatively late when patients already show clinical or imaging signs of advanced herniation. Considering our findings that any kind of developing mass effect was predictive for poor outcome, one might speculate that earlier decompressive surgery might be even more effective than already suggested by the existing case series.

Whether treatment with local thrombolysis or thrombectomy in severely affected CVT patients could help to avoid space-occupying lesions and improve outcome cannot be answered by our results and will hopefully be shown by the ongoing prospective randomized *To-Act* trial [20].

We are aware of several limitations of our study. The retrospective design of the study and the fact that it covers a long time period might impair data quality. For example, in 25 patients, imaging datasets could not be made available. Potential sources of bias are incomplete case ascertainment, dependence on clinical coding systems for retrospective chart reviews, and the absence of a uniform treatment is a further limitation. Another potential bias could be that all participating centers were tertiary care hospitals with neurointensive care units, probably treating more severe cases and being more experienced in the treatment of severe CVT than other hospitals thus limiting generalizability. We would like to stress the explorative character of this study and the fact that we did not correct the p values for multiple testing.

Still, this is to date the largest analysis of patients with severe CVT and its strengths are a systematical, protocolized approach to assessment of pre-defined variables, a centralized radiological work-up, and the very low number of patients lost to follow-up. To collect larger samples of severe CVT is challenging since it is such a rare disease and prospective studies on this subgroup of CVT patients are either lacking or very small: Out of 624 patients included in the ISCVT study, only 31 were comatose. At present, best evidence comes from case series and as long as results from prospective trials on this rare clinical entity are lacking, we might have to rely on retrospective studies such as the present one.

Conclusions

The outcome of patients with severe CVT requiring critical care is worse than the overall outcome of all patients with CVT with more than half of the patients dying or remaining dependent. On the other hand, survival with no or only mild deficits can be achieved in almost half of the patients. Poor outcome is determined particularly by imaging signs of mass effect and associated neurologic deterioration during the clinical course. Therefore, we suggest that

patients with severe CVT should receive maximal ICU treatment from the onset, should be monitored closely to detect any signs of space-occupying mass effect as early as possible to enable early escalative treatment of mass effect, and prevent clinical deterioration and poor outcome. Of the escalative treatment options, decompressive hemicraniectomy is best described, but optimal treatment options to prevent and treat developing mass effect still remain to be elucidated prospectively.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from individual participants if they were contacted in order to obtain follow up information especially for this study. For retrospective data acquisition formal consent is not required.

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