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ORIGINAL COMMUNICATION

Long-term outcome after cerebral venous thrombosis: analysis of functional and vocational outcome, residual symptoms, and adverse events in 161 patients

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Abstract Cerebral venous thrombosis (CVT) affects mainly working-aged individuals. Functional recovery after CVT is generally considered good with about 3/4 of patients achieving short-term independence. However, vascular events, long-term functional outcome, and employment after CVT remain poorly investigated. We identified consecutive adult CVT patients treated at the Helsinki University Hospital (1987–2013) and invited them to a follow-up visit. Each clinical examination was combined with interview. We also recorded recurrent venous thromboembolism (VTE) and hemorrhagic events during follow-up and antithrombotic medication use. A modified Rankin Scale (mRS) served to assess functional outcome. Logistic regression served to identify independent factors associated with unemployment and functional recovery. Of the 195 patients identified, 21 died, 9 declined to participate, and 4 were excluded from the study. Thus, 161 patients (106 women) underwent an examination after a median of 39 months (interquartile range 14–95). VTE (one of which was CVT) occurred in 9 (6 %) patients, and severe hemorrhagic events in 10 (6 %). Functional outcome was good, with 84 % scoring 0–1 on the mRS; 42 % reported residual symptoms. Altogether, 91 (57 %) patients were employed. After adjusting for age and sex, a National Institutes of Health Stroke Scale score >2 at admission and low education level, associated with both unfavorable functional outcome and unemployment. Long-term functional outcome after CVT may appear good if measured with mRS, but patients often have residual symptoms and are frequently unable to return to their previous work.

Keywords Cerebral venous thrombosis · Sinus thrombosis · Long-term outcome · Anticoagulation · Follow-up · Vocational status

Introduction

Cerebral venous thrombosis (CVT) is a rare disease that affects mainly working-aged individuals and is more common among women. Symptoms of the disease vary: 90 % present with headache, 40 % motor or sensory deficits, and 40 % epileptic seizures. Over half of patients develop parenchymal lesions [1]. Short-term mortality is <10 %, and the vast majority of patients regain independence in daily living [2, 3].

The largest dataset on outcome after CVT is available from the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), a multinational study with 624 patients monitored over a relatively short period (mean 16 months). That study focused on death and dependency at the time of follow-up: 8 % died, and 80 % recovered well (defined as a score of 0–1 on the modified Rankin Scale (mRS)) [1]. In the ISCVT cohort, the recurrence of venous thromboembolism was 4/100 patient-years, and

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CVT recurrence was 1.5/100 patient-years [4]. The risk for thrombotic event recurrence appears to be highest in the first year after diagnosis [4–6]. Women with a history of CVT may be at elevated risk for miscarriage, but outcome does not otherwise differ from that of the general population [7, 8]. Relatively few small studies have investigated long-term outcome (beyond 1–2 years) after CVT [9–15].

Study objectives

The aims of our study were to investigate long-term functional outcome, residual symptoms, and working ability after CVT in a large single-center patient population. We also explored their risk for recurrent venous thromboembolism (VTE), antithrombotic medication use, risk for bleeding events, and reproductive health.

Patients and methods

The appropriate institutional authorities and Ethics Board approved this study, which was conducted by the Department of Neurology, Helsinki University Hospital (HUH). Our study included all consecutive patients over the age of 16 treated in the HUH area for CVT between January 1987 and August 2013. We invited all patients for a follow-up visit at least 6 months after diagnosis. Each participant provided written consent.

Baseline characteristics

We examined patient records extensively and recorded clinical presentation, etiological and risk factors, laboratory testing, imaging studies, clinical findings, and treatments. We also reconstructed the Admission National Institutes of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS) from medical records notes. According to our institutional guidelines, an NIHSS score of 0–2 represented minor stroke symptoms. We recorded education level in three categories: primary (compulsory education of 9 years), secondary (high school or equivalent), and tertiary (university) education. We recorded primary education only as low education level. We also recorded working status at the time of CVT diagnosis.

Long-term outcome evaluation

We developed a structured questionnaire to assess long-term outcome. Questions inquired about education, working status, current medication, residual symptoms (epileptic seizures, headache, visual disturbances, motor and sensory deficits, memory and concentration difficulties fatigue, and linguistic difficulties) type and duration of anticoagulation treatment, severe bleeding complications, recurrent venous thromboembolism, any sickness leading to hospitalization, and health history. We also recorded the use of oral contraceptives and hormonal replacement therapy, as well as status of subsequent pregnancies (miscarriages, complications, and anticoagulation use). Patients also responded to the Beck Depression Inventory which screens for depression. We evaluated outcome at least 6 months after initial CVT diagnosis in two patients by mailed questionnaires, and in the rest by questionnaires combined with clinical examination. We verified all responses and resolved any unclear/equivocal responses by interviewing patients face-to-face and reviewing their medical records. Clinical examination included assessment with the modified rankin scale (mRS), NIHSS score, and Barthel index.

Main outcome measures

The primary outcome measures were recovery, as measured with the mRS, and working status at the end of the follow-up period. A favorable outcome was defined as mRS 0-1, indicating complete recovery or only mild residual symptoms not affecting everyday life.

We dichotomized working status as employed and unemployed. We excluded persons who were retired for reasons unrelated to CVT (old age $n = 26$; underlying illness $n = 9$) from the return-to-work analysis as well as women on maternity leave ($n = 5$), due to uncertainty about their ability to return to their previous employment. We categorized those working part-time but over 50 % of standard working hours ($n = 2$) and students ($n = 7$) as employed.

Statistical analyses

We considered demographic factors, clinical and imaging findings, and known risks as possible explanatory factors for patients' outcomes. We calculated univariate odds ratios (OR) and 95 % confidence intervals (CI) for each individual variable. Binary logistic regression analysis served to investigate independent factors associated with unfavorable outcomes and patients' return to work. We entered into the multivariate model variables showing a univariate association with $P < 0.10$, and further adjusted them for age and sex. A two-sided P value <0.05 was considered significant. SPSS 22 for Windows (Armonk, NY, USA) served to analyze all data.

Results

We identified 195 consecutive patients with a CVT diagnosis. Of these, 21 patients (11 %) died, 9 patients (5 %) declined to participate, 1 patient moved to another country

and was lost to follow-up, 1 patient's CVT diagnosis was revoked (the final diagnosis was acute cytomegalovirus infection with sinus hypoplasia), and 2 patients were excluded due to missing patient records. Thus, 161 patients remained for examination at follow-up (106 females, 67 %); Fig. 1. The median follow-up period was 39 months (IQR 14-95), yielding a total of 818 patient-years. The median age at diagnosis was 38 years (IQR 27-54), and at follow-up 45 years (IQR 33-60). The baseline data on the patients appear in Table 1.

Deceased patients

Of the 21 patients who died, 7 died from direct consequences of the index CVT (4 patients died within 6 months of diagnosis), 7 from underlying malignancy, 2 from coronary artery disease, 1 from pulmonary fibrosis, and 1 from dementia; in 3 patients, the cause of death remained unknown (1 lacked data, 2 were sudden deaths).

Antithrombotic medication, recurrent VTEs, and hemorrhagic events

In the acute phase, 154 (96 %) patients received heparin, 1 patient began treatment with warfarin, and 5 patients underwent treatment without anticoagulants. By the end of the follow-up period, 47 patients (29 %) used no antithrombotic medication. A total of 56 (35 %) patients received oral anticoagulants, 9 (6 %) low-molecular-weight heparin, 40 (25 %) aspirin, and 10 (7 %) patients a combination of medications; 62 patients (39 %) received permanent anticoagulation.

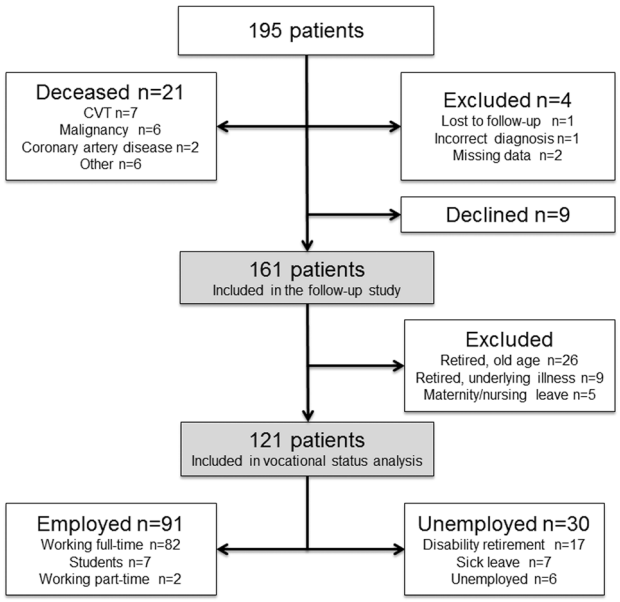

Fig. 1 Patient flow chart

Table 1 Baseline data on the 161 patients with cerebral venous thrombosis (CVT)

Demographic data	
Female	106 (67)
Age at CVT onset	38 years (24–54)
Follow-up period	39 months (14–95)
Risk factors	
Local infection	19 (12)
Malignancy	10 (6)
Any coagulation disorder	34 (21)
Any systemic prothrombotic disorder	25 (16)
Trauma	5 (3)
Neurosurgery	0
No known risk factor	15 (9)
Pregnancy or puerperium in women	5 (3)
Estrogen use in women	39 (24)
Clinical findings at admission	
Headache	136 (84)
Motor or sensory deficit	52 (32)
Seizure	49 (30)
Any focal symptom ± encephalopathy	9 (58)
Headache only or IIH*	50 (31)
Glasgow coma scale 12 or lower	10 (6)
NIHSS† score >2	31 (19)
Neuroimaging at admission	
Infarction	34 (21)
Hemorrhagic lesion	22 (14)
Deep cerebral vein thrombosis	12 (7)
Hydrocephalus	11 (7)

Data appear as *n* (%) or median (interquartile range)

* Isolated intracranial hypertension

† National Institutes of Health Stroke Scale

Recurrent VTE occurred in nine patients (6 %): five deep vein thromboses, two pulmonary embolisms, and three superficial vein thromboses. The incidence of VTE was 1.1/100 person-years, and CVT recurred in one patient (incidence 0.1/100 person-years). We noted ten hemorrhagic events requiring medical attention, four of which were potentially life-threatening (4 intracranial bleedings, 2 of which were traumatic), although none was fatal. For detailed information on thrombotic and bleeding events, please see Online resource 1.

Reproductive health

During the follow-up period, 23 pregnancies and 5 spontaneous miscarriages occurred, but no patients experienced thrombotic events or complications during pregnancy or the puerperal period. Only two women did not use antithrombotic medication during pregnancy (19 patients

used low-molecular-weight heparin, and 2 patients used aspirin).

Functional outcome

Functional outcome was good in 82 % of patients scoring 0–1 on the mRS. Modified Rankin scores in different patient groups appear in Fig. 2. Six patients (4 %) required assistance in activities of daily living, (scoring below 100 points on the Barthel index). As many as 68 % of patients reported residual symptoms, the most common of which were neuropsychological difficulties (41 %), linguistic difficulties (21 %), headache more than once a week (20 %), and depression (19 %) (Beck depression inventory >13 points); Table 2.

In univariate analysis, baseline factors associated with unfavorable outcome (mRS ≥2) were male sex, low education level, focal symptoms, NIHSS score >2, and hemorrhagic lesion in magnetic resonance imaging (MRI), whereas isolated intracranial hypertension or isolated headache associated with favorable outcome (Table 3). In female patients, estrogen use (oral contraceptives or hormone replacement therapy) associated with unfavorable outcome.

After entering the factors with univariate $P < 0.10$ into the logistic regression model and further adjusting them for age and sex, NIHSS score >2 (OR 5.8, CI 2.2–15.6, $P < 0.001$) and low educational level (OR 4.8, CI 1.3–17.4, $P = 0.016$) independently associated with unfavorable outcome.

Vocational outcome

At the time of follow-up, 91 (57 %) of patients were employed. Seven patients (4 %) were employed at the time of CVT diagnosis, but had retired due to their age. We found no significant difference in follow-up length between the employed and unemployed. Factors related to employment appear in Table 4. In univariate analysis, all recorded residual symptoms except headache associated with unemployment. Other factors associated with employment status were male sex, age >38 years, low education level, coagulation disorder, and NIHSS score >2. After adjusting these risk factors for age and sex, low education (OR 4.8, CI 1.0–21.2, $P = 0.046$) and NIHSS score >2 (OR 3.2, CI 1.1–10.9, $P = 0.029$) associated with working status.

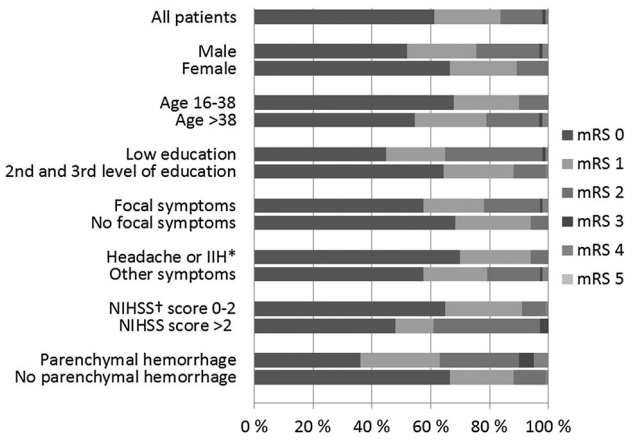

Fig. 2 Modified rankin scale distribution by selected patient groups. *Asterisk* isolated intracranial hypertension, *dagger symbol* National Institutes of Health Stroke Scale

Table 2 Thrombotic events, antithrombotic medication and residual symptoms at follow-up in 161 patients with cerebral venous thrombosis

Venous thrombotic event recurrence	9 (6)
Recurrent cerebral venous thrombosis	1 (1)
Deep vein thrombosis	5 (3)
Pulmonary embolism	2 (1)
Superficial vein thrombosis	3 (2)
Anticoagulation at follow-up	
Permanent anticoagulation in use	62 (39)
Anticoagulation length	6 months (6–12)
No antithrombotic drugs	47 (29)
Low-molecular-weight heparin	9 (6)
Oral anticoagulant (warfarin)	56 (35)
Aspirin	40 (25)
Combination of medications	10 (6)
Hemorrhage requiring medical help	10 (6)
Residual symptoms	
Headache >1/week	33 (20)
Motor and/or sensory deficit	11 (6)
Linguistic difficulties	34 (21)
Neuropsychological symptoms, self-reported	66 (41)
Impaired vision	20 (12)
Active epilepsy	15 (9)
Depression	30 (19)
Received neuropsychological rehabilitation	28 (17)

Data appear as *n* (%) or median (interquartile range)

Discussion

Our study provides data on various aspects of long-term outcome in a large singe-center series of CVT patients. The recurrence risk for VTE was low. Almost all our patients were independent, and 82 % had a favorable outcome (mRS 0-1). However, despite apparently good functional outcome, the majority of our patients reported residual symptoms.

Table 3 Long-term functional outcome in CVT patients

	mRS* 0-1 ($n = 133$)	mRS 2-5 ($n = 23$)	OR	95 % CI	*P*
Demographic data					
Male sex	39 (29 %)	14 (56 %)	3.07	1.28–7.35	0.009
Age >38	62 (47 %)	17 (68 %)	2.43	0.98–6.02	0.050
Low education level	16 (12 %)	10 (40 %)	4.83	1.86–12.5	0.001
Risk factors					
Local infection	18 (14 %)	1 (4 %)	0.27	0.03–2.10	0.181
Malignancy	8 (6 %)	2 (8 %)	1.36	0.27–6.81	0.711
Any systemic disorder	22 (17 %)	3 (12 %)	0.68	0.19–2.48	0.562
Any coagulation disorder	29 (25 %)	5 (24 %)	0.91	0.31–2.69	0.859
Trauma	3 (2 %)	2 (8 %)	3.91	0.62–24.75	0.123
Neurosurgery	0	0	NA	NA	NA
No known risk factor	11 (15 %)	4 (24 %)	1.65	0.45–6.01	0.450
Pregnancy/puerperium in women	4 (4 %)	1 (9 %)	2.22	0.23–21.90	0.487
Estrogen use in women	31 (33 %)	8 (73 %)	5.33	1.32–21.52	0.010
Clinical findings at admission					
Focal symptoms ± encephalopathy	75 (57 %)	19 (79 %)	2.88	1.01–8.20	0.040
Headache only or IIH†	47 (35 %)	3 (13 %)	0.25	0.07–0.87	0.029
GCS‡ 12 or lower	7 (5 %)	3 (12 %)	2.56	0.61–16.64	0.190
NIHSS§ score >2 at admission	19 (15 %)	12 (52 %)	6.31	2.40–16.40	<0.001
Neuroimaging at admission					
Infarction	27 (20 %)	7 (30 %)	1.53	0.58–4.03	0.393
Hemorrhagic lesion	14 (11 %)	8 (35 %)	4.00	1.46–10.94	0.007
Deep cerebral vein thrombosis	8 (6 %)	4 (16 %)	2.98	0.82–10.80	0.090
Hydrocephalus	2 (2 %)	2 (9 %)	5.70	0.76–42.78	0.090
Intracranial bleeding during anticoagulation treatment	2 (2 %)	2 (9 %)	5.70	0.76–42.48	0.090

* Modified rankin scale

† Isolated intracranial hypertension

‡ Glasgow coma scale

§ National Institutes of Health Stroke Scale

Our findings on mortality and functional outcome are similar to the results of the largest study on CVT study to date, the ISCVT with <10 % mortality and 80 % of patients achieving good functional recovery (mRS 0-1). Dependency (mRS >2) was very rare, with only 2 % of patients requiring help in daily activities. It is notable that in our study population, more patients presented with headache or isolated intracranial hypertension than in the ISCVT cohort (31 vs. 12 %); parenchymal lesions were also less common in our study population (33 vs. 63 %). This difference may be due to greater accessibility to MRI in recent years, which may have increased the number of patients presenting with less severe symptoms [1]. Our findings of age, male sex, and intracerebral hemorrhage in MRI as predictors of poor functional outcome, and of the clinical presentation of headache/isolated intracranial hypertension as a predictor of good functional recovery confirm those of previous reports [1, 16].

The recurrence of venous thromboembolism in our study was lower than that observed in previous studies in which 6 % of patients suffered from VTE (incidence 1.1/100 patient-years) and CVT recurred only once. The ISCVT cohort and a smaller study of 154 patients observed a VTE incidence of 4–5/100 patient-years and a CVT incidence of 1.5–2.2/100 patient-years [4, 6]. One study with 145 patients and a six-year follow-up period after cessation of anticoagulation reported an incidence of CVT of 0.5/100 patient-years, and of VTE, 2.0/100 patient-years. However, this study did not include patients with malignancies or in need of permanent anticoagulation [5]. The low incidence of recurrent VTE in our study may be due to our patients' frequent use of antithrombotic drugs, as 39 % of our patients received permanent anticoagulation medication, and 25 % received aspirin. In previous studies, the frequency of permanent anticoagulant use was considerably lower (22 and 16 %) [4, 5]. Our institutional

Table 4 Vocational outcome among 121 working-aged patients with cerebral venous thrombosis

	Employed ($n = 91$)	Unemployed ($n = 30$)	OR	95 % CI	*P*
Demographic data					
Sex, male	22 (24 %)	13 (43 %)	1.28	0.97–1.67	0.048
Age >38 years at CVT* diagnosis	29 (32 %)	17 (57 %)	2.80	1.20–6.52	0.017
Low education level	84 (93 %)	19 (63 %)	6.63	1.11–20.86	0.001
Employed before CVT diagnosis	61 (67 %)	16 (53 %)	2.06	0.86–4.93	0.103
Follow-up period (mean)	60 months	70 months	1.00	1.00–1.01	0.420
Risk factors					
Local infection	10 (11 %)	6 (20 %)	2.03	0.67–6.14	0.213
Any infection	12 (13 %)	5 (17 %)	1.32	0.42–4.10	0.635
Malignancy	3 (3 %)	2 (7 %)	2.10	0.33–13.18	0.431
Any systemic disorder	13 (14 %)	4 (13 %)	1.00	0.27–3.04	0.880
Any coagulation disorder	23 (25 %)	2 (7 %)	0.21	0.05–0.96	0.043
Dehydration	12 (13 %)	4 (13 %)	1.00	0.30–3.37	1.000
Trauma	3 (3 %)	1 (3 %)	1.01	0.10–10.11	0.992
Neurosurgery	0	0	NA	NA	NA
No known risk factor	7 (8 %)	4 (13 %)	2.29	0.56–9.37	0.251
Estrogen use in women	54 (78 %)	9 (53 %)	0.31	0.10–0.95	0.040
Clinical findings at admission					
Focal symptoms ± encephalopathy	51 (56 %)	22 (73 %)	2.10	0.85–5.22	0.109
Headache or IIH†	35 (38 %)	7 (23 %)	0.51	0.19–1.32	0.163
NIHSS‡ score >2	11 (12 %)	11 (37 %)	4.05	1.53–10.74	0.005
GCS§ 12 or lower	6 (7 %)	2 (7 %)	1.00	0.19–5.24	1.000
Neuroimaging at admission					
Infarction	20 (22 %)	9 (30 %)	1.52	0.60–3.83	0.374
Hemorrhagic lesion	8 (9 %)	4 (13 %)	1.59	0.44–5.73	0.473
Deep cerebral vein thrombosis	7 (8 %)	4 (13 %)	1.85	0.50–6.80	0.357
Hydrocephalus	2 (2 %)	3 (10 %)	4.94	0.79–31.14	0.089
Symptoms at follow-up					
Headache >1 times/week	9 (10 %)	4 (13 %)	1.01	0.23–4.44	0.983
Motor and/or sensory deficit	4 (4 %)	5 (17 %)	4.53	1.13–18.20	0.033
Linguistic problems, self-reported	12 (13 %)	17 (57 %)	9.33	3.58–24.27	<0.001
Neuropsychological problems, self-reported	21 (23 %)	22 (73 %)	10.48	3.93–27.93	<0.001
Impaired vision	7 (8 %)	7 (23 %)	4.00	1.27–12.65	0.018
Active epilepsy	2 (2 %)	7 (23 %)	29.33	3.42–251.42	0.002
Depression	11 (12 %)	10 (30 %)	3.54	1.31–9.56	0.013
Intracranial bleeding during anticoagulation treatment	2 (2 %)	0	0.00	NA	0.385

* Cerebral venous thrombosis

† Isolated intracranial hypertension

‡ National Institutes of Health Stroke Scale

§ Glasgow coma scale

guidelines recommend permanent anticoagulation for patients with recurrent venous thrombosis, thrombophilia, or a significant non-transient risk factor for venous thrombosis; for others, guidelines recommend 6–12 months of anticoagulation. No institutional guidelines are available for aspirin use, but doctors often prescribe aspirin to patients with no obvious or transient risk factors. Aspirin use may play a role in lowering the incidence of VTE, as aspirin reduces the risk for venous thrombosis by 42 % [17]. Despite the high number of patients using anticoagulation medication, only 6 % of them reported bleeding events requiring medical help (incidence 1.3/100 patient-years). The relatively young age of CVT patients may explain the low incidence of bleeding events. Notably,

subsequent pregnancies after CVT were uneventful, with no thrombotic complications. Our findings are in line with those of previous studies emphasizing that a history of CVT is no contraindication to future pregnancies [7, 8].

In our study, 68 % of patients reported residual symptoms years after their CVT diagnosis. We found a 10 % rate of active epilepsy, similar to that in previous studies [1, 10, 12]. As many as 20 % of our patients reported suffering from headache more than once a week; in previous studies, the prevalence of residual headache has varied widely from 10 to 50 %, depending on the definition [1, 9, 11, 12]. Although a large number of patients reported linguistic and neuropsychological problems, our study unfortunately provided no detailed neuropsychological testing. Three studies with robust cognitive testing showed abnormal findings in 18–34 % of the patients [13, 14, 18]. In our study, one in five patients showed signs of depression, thus supporting the finding of two studies that depression is common among CVT patients [14, 15]. Our study strengthens the notion that patients recover well from paresis, with only one in ten suffering from motor or sensory deficits [10, 12, 14]. Other neurological residual symptoms, however, were common. Interestingly, we observed that low education level and an NIHSS score over two points strongly associated with both incomplete functional recovery and diminished working ability. Education level may influence motivation and adherence to rehabilitation, motivation to return to work, or pose an obstacle to finding suitable employment. The NIHSS score used in arterial stroke is reliable clinical measurement method, showing high correlation with outcome and the size of parenchymal damage [19]. Our findings that the NIHSS score also correlates with outcome in CVT suggest that the NIHSS score could prove useful in early screening of patients at risk for unfavorable outcome.

Only small studies have previously explored working ability after CVT. In one study with 34 CVT patients, all recovered without functional disability and resumed their work [14]. In two other studies, 20–40 % of CVT patients failed to resume full-time employment [13, 18]. In our study, 25 % of working-age CVT patients were unemployed at the end of the follow-up period, and 16 % received permanent disability pension. Of course, non-medical issues, such as general economic climate and national sick retirement benefits and rules, also affect employment rates. Our study suggests that even though patients after CVT recover well functionally, residual symptoms that affect working ability are common.

Our study has strengths and limitations. Our study is among the largest published single-center series on CVT outcome thus far, with a respectable follow-up period and a high participation rate. The study's weaknesses mainly arise from its retrospective nature, as the long follow-up period may have created a selection bias in that early CVT patients presented with more severe disease. The retrospective study design may also have led to reporting bias on cognitive symptoms and minor bleeding events during follow-up, so readers should exercise caution with our conclusions about anticoagulation safety. Another weakness is the study's lack of neuropsychological testing and its reliance on patient-reported symptoms.

Conclusions

Our study reinforces the finding that long-term outcome after CVT is good, with the majority of patients achieving independence and a low risk for recurrent venous thromboembolism with the use of antithrombotic medication. However, many of our patients suffered from residual symptoms, and a substantial proportion remained unable to return to working life.

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Compliance with ethical standards

Conflicts of interest None.

Ethical standards All human studies must state that they have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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