

# Cerebral Venous Thrombosis in the Absence of Headache

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on behalf of the ISCVT Investigators

**Background and Purpose**—Although headache is the most common symptom in cerebral venous thrombosis, 5% to 30% of patients do not report headache at baseline. Characteristics of these patients have not been investigated.

**Methods**—In post hoc analysis of the International Study on Cerebral Vein and Dural Sinus Thrombosis study, patients who might not have been able to report headache (aphasia, stupor, coma, or mental status disorder) were excluded.

**Results**—Three hundred eighty-two of the original 624 patients (61%) were included, of whom 38 (10%) did not report headache at baseline. Patients without headache were older (mean age, 45 versus 37;  $P=0.001$ ) and less often female (63% versus 77%;  $P=0.06$ ). Paresis (42% versus 27%;  $P=0.05$ ) and seizures (58% versus 32%;  $P=0.001$ ) were more common in patients without headache, whereas papilledema was less common (8% versus 35%;  $P=0.001$ ). Isolated cortical vein thrombosis (16% versus 2%;  $P=0.001$ ), brain parenchymal lesions (66% versus 46%;  $P=0.02$ ), and malignancies (18% versus 6%;  $P=0.009$ ) were more common among patients without headache. Outcome at last follow-up was worse in patients without headache (modified Rankin Scale, 0–1; 76% versus 89%;  $P=0.04$ ; mortality, 13% versus 5%;  $P=0.05$ ), but after adjustment for prognostic variables, headache was not an independent predictor of outcome.

**Conclusions**—Patients with cerebral venous thrombosis but without headache are a heterogeneous subgroup, in which older patients, men, and some associated conditions are over-represented. Patients without headache had a worse clinical outcome, but after adjustment for imbalances, headache was not an independent predictor of outcome. (*Stroke*. 2015;46:245-247. DOI: 10.1161/STROKEAHA.114.007584.)

**Key Words:** headache ■ intracranial sinus thrombosis ■ venous thrombosis

Headache is the most common and usually the first symptom in patients with cerebral venous thrombosis (CVT).<sup>1</sup> Still, various cohort studies indicate that 5% to 30% of patients do not report headache at baseline.<sup>1–3</sup> Details of this subgroup of patients have never been examined. It is even doubtful how many of such patients really exist, as they may have been unable to report headache, for instance because of decreased consciousness or aphasia. The aim of our study was to examine the characteristics of patients with CVT without headache.

## Methods

We used data from the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT).<sup>1</sup> ISCVT was a prospective international cohort study of 624 patients with CVT. For the present study, we excluded patients who might not have been able to report headache because 1 of the following signs was present: aphasia, mental status disorder, stupor, or coma. We included these patients in a separate analysis to test the hypothesis that headache is underreported in patients with a disturbance of consciousness or language. We analyzed data with the  $\chi^2$ , Fisher exact test, or Mann–Whitney test, whichever was appropriate. Logistic regression analysis was used to determine

whether absence of headache was an independent predictor of outcome. We corrected for all variables that were associated with clinical outcome in the primary analysis of the ISCVT (age, sex, intracranial hemorrhage, central nervous system [CNS] infection, cancer, and thrombosis of the deep venous system).<sup>1</sup>

## Results

Of the 624 patients included in ISCVT, 382 (61%) were included in the analysis (Figure). Reasons for exclusion were as follows: no data on headache ( $n=1$ ), aphasia ( $n=119$ ), stupor or coma ( $n=87$ ), and mental status disorder ( $n=137$ ). One hundred two patients had >1 reason for exclusion. Of the 382 patients, 38 (10%) did not have headache at baseline. There was no significant difference in the reported frequency of headache between included patients and those who were excluded because of disturbance of consciousness or language (10% versus 13%;  $P=0.20$ ).

Compared with patients with headache, those without headache were older (45 versus 37 years;  $P=0.001$ ), less often female (63% versus 77%;  $P=0.06$ ), and had shorter interval from onset of symptoms to admission (2 versus 6 days;

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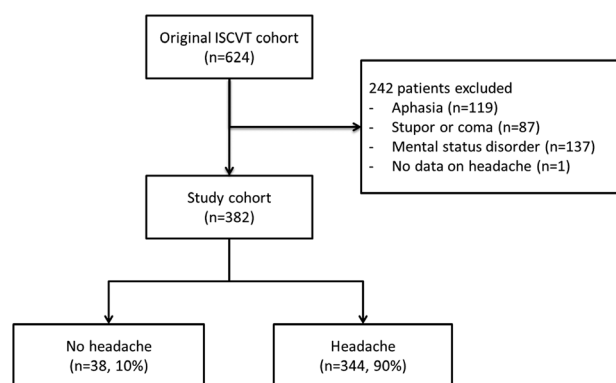
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**Figure.** Flowchart of patient selection. ISCVT indicates International Study on Cerebral Vein and Dural Sinus Thrombosis.

$P=0.002$ ; Table 1). Paresis (42% versus 27%;  $P=0.05$ ) and seizures (58% versus 32%;  $P=0.001$ ) were more common in patients without headache, whereas papilledema was less common (8% versus 35%;  $P<0.001$ ). Isolated cortical vein thrombosis (16% versus 2%;  $P<0.001$ ) and brain parenchymal lesions (66% versus 46%;  $P=0.02$ ) were found more often in patients without headache. Patients without headache less often had thrombosis of multiple sinuses (26% versus 53%;  $P=0.002$ ), and percentages of thrombosis of the superior sagittal, sigmoid, transverse, and straight sinus were all lower among patients without headache (data not shown).

The risk factors, cancer (18% versus 6%;  $P=0.009$ ), infection of CNS (5% versus 2%;  $P=0.1$ ), and iatrogenic CVT (21% versus 9%;  $P=0.04$ ) were more common among patients without headache, whereas oral contraceptive use was lower (21% versus 53%;  $P=0.003$ ; Table 2). The higher proportion of cancer was attributable to an overrepresentation of CNS malignancies (13% versus 1%;  $P=0.001$ ). Outcome at last follow-up was worse in patients without headache (modified Rankin Scale, 0–1: 76% versus 89%;  $P=0.04$ ; mortality, 13% versus 5%;  $P=0.05$ ), but after adjustment for known prognostic variables, absence of headache was not an independent predictor for outcome.

**Table 1. Baseline Characteristics**

	No Headache (n=38)	Headache (n=344)	P Value
<b>Clinical characteristics</b>			
Median age (IQR), y	42 (33–56%)	35 (25–47%)	0.002
Sex (female)	24/38 (63%)	265/344 (77%)	0.06
Median days onset admission (IQR)	2 (0–8%)	6 (2–14%)	0.002
Paresis	16/38 (42%)	93/344 (27%)	0.05
Seizures	22/38 (58%)	110/344 (32%)	0.001
Papilledema	3/36 (8%)	117/339 (35%)	<0.001
<b>Radiological findings</b>			
Isolated cortical vein thrombosis	6/38 (16%)	7/343 (2%)	<0.001
Brain parenchymal lesion*	25/38 (66%)	156/343 (46%)	0.02
Thrombosis $\geq 2$ sinus	10/38 (26%)	182/343 (53%)	0.002

IQR indicates interquartile range.

\*Intracerebral hemorrhage and nonhemorrhagic infarct.

**Table 2. Risk Factors, Treatment, and Outcomes**

	No headache (n=38)	Headache (n=344)	P Value
<b>Risk factors</b>			
Oral contraceptives*	5/24 (21%)	140/265 (53%)	0.003
Pregnancy/puerperium*	5/24 (21%)	36/265 (14%)	>0.1
Cancer	7/38 (18%)	19/344 (6%)	0.01
CNS malignancy	5/38 (13%)	4/344 (1%)	0.001
CNS infection	2/38 (5%)	5/344 (2%)	0.1
Iatrogenic†	8/38 (21%)	32/344 (9%)	0.04
<b>Treatment and outcomes</b>			
Anticoagulation	31/38 (82%)	291/344 (85%)	>0.1
mRS, 0–1	29/38 (76%)	305/344 (89%)	0.04
mRS, 3–6	6/38 (16%)	25/344 (7%)	0.1
Mortality	5/38 (13%)	16/344 (5%)	0.05

CNS indicates central nervous system; and mRS, modified Rankin Scale.

\*Percentage of women.

†Cerebral venous thrombosis caused by lumbar puncture, (neuro) surgical intervention, drugs, or central venous line.

## Discussion

This is the first study of the characteristics of patients with CVT without headache. We had anticipated that after exclusion of patients who might not have been able to report headache, the proportion of patients without headache would have been much smaller, as has been suggested previously.<sup>4,5</sup> Instead and surprisingly, the percentage we found (10%) was not significantly lower than in the excluded patients.

There may be a variety of reasons why certain patients with CVT do not have headache, as is suggested by the heterogeneous composition of this subgroup. Patients with isolated cortical vein thrombosis, for instance, were overrepresented. A systematic review of the literature showed that these patients less often have headache, most likely because intracranial hypertension and distension of the sinuses are less common.<sup>6</sup> The older age of patients without headache may also be an explanatory factor.<sup>7</sup> An inverse association between headache and age has been found in other cerebrovascular disorders.<sup>8,9</sup> Patients without headache also more often had seizures. Some of these patients might not recall a headache that occurred before the seizure.

The association between oral contraceptives use and headache among patients with CVT has been shown previously.<sup>10</sup> In contrast, the fact that patients without headache more often had an infection or malignancy of the CNS is surprising because even in the absence of CVT, many of these patients, especially those with an infection, have a headache.<sup>11</sup> Possibly, these patients did not report headache because they had already received analgesics.

Patients without headache had a worse outcome at follow-up, but multivariate analysis showed that the difference in outcome is explained by a worse clinical condition at baseline and an overrepresentation of severe underlying diseases (cancer and CNS infections). Strengths of this study are the large number of patients, the completeness of the data set, and the fact that we limited our analysis to those patients who were able to report headache. The data were collected prospectively, but

the present study question was not one of the predefined aims. Therefore, additional information, such as whether some of the patients developed headache later in the course of the disease, is not available. Despite our efforts to minimize patient response bias by excluding patients who might not have been able to report headache, we cannot exclude the possibility of a residual bias. Patients with severe clinical manifestations, which were more common in patients without headache, may be less likely to report less severe symptoms, such as headache. Also a physician may be less likely to take a complete clinical history in such patients.

In conclusion, we found that patients with CVT but without headache are a heterogeneous subgroup, in which older patients, men, and some associated conditions are overrepresented. Patients without headache had a worse clinical outcome, but after adjustment for imbalances, headache was not an independent predictor of outcome.

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### Disclosures

None.

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