Clinical characteristics of cerebral venous sinus thrombosis patients with new-onset of headache

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Abstract

Objective This study aimed to assess the clinical characteristics of cerebral venous sinus thrombosis (CVT) patients with new-onset headache and to identify the risk factors for headache in this population.

Methods We retrospectively reviewed the demographic and clinical data of 69 CVT patients recruited between September 2017 and September 2019. Patients were classified into two groups, the headache group and the non-headache group, according to the presence or absence of new-onset headache symptoms at admission. The following characteristics and parameters were measured and analyzed, including gender, age, amount of thromboembolic cerebral venous sinus (ATCVS), and other relevant indicators.

Results The incidence of headache was 75% in this cohort. The proportion of female patients in the headache group was higher than that in the non-headache group. Patients in the headache group were younger than those without headache. CVT patients of headache group showed higher lymphocyte ratio (LR), blood urea nitrogen (BUN), and intracranial pressure (ICP) compared to the non-headache group, whereas mean corpuscular volume (MCV) and levels of protein (cerebrospinal fluid, CSF) and lactic dehydrogenase (LDH) in CSF were lower in headache patients. The data also revealed younger age and the increased level of chloride ion Cl-(CSF) were the risk factors for the occurrence of headache in CVT patients.

Conclusion Age, LR, MCV, BUN levels, ICP, protein (CSF), and LDH (CSF) in patients with headache were significantly different from those in the non-headache group at admission. Younger age and a level of CI- (CSF) were risk factors for headache in CVT patients. These findings may provide guidance for clinical diagnosis and treatment of CVT.

Keywords Cerebral venous thrombosis, Clinical characteristics analysis, Headache, Clinical diagnosis

Introduction Cerebral venous thrombosis (CVT) is an uncommon cerebrovascular disease that accounts for 0.5–2% of all stroke cases [1]. Patients with CVT often present with various symptoms including headache, dizziness, vomiting, nausea, seizures, unconsciousness, and unresponsiveness. CVT is also a rare, life-threatening disease that may cause sudden death [2]. It may occur in all age groups [3] and females are three times more likely to be diagnosed with CVT than males [4, 5]. The risk factors for CVT include infectious diseases (e.g. head and face
infection) and non-infectious factors, such as hypercoagu-
ability, blood stasis, head and neck trauma, oral contra-
ceptive drugs, hormone replacement therapy, pregnancy
[6] and low intracranial pressure [2]. No underlying risk
factor is found in approximately 13% of CVT patients
[7]. Current treatments for CVT include anticoagulation
therapy, symptomatic therapy, and etiological treatment.
Intravascular intervention may be applied to patients
with severe CVT [8]. With the improvement in imaging
diagnostic techniques and early treatment with antico-
agulation, the mortality rate of CVT has decreased over
the past years [9].

Headache is a common manifestation present in over
85% of CVT patients. However, there are limited studies
that investigate the association between clinical charac-
teristics of CVT patients and the occurrence of headache.
The pathological mechanism of CVT-related headache
may involve the stretching and compression of occluded
venous sinuses, which lead to increased ICP and eventual-
ly pain in the head.

Different types of headaches have been observed
in CVT patients, including exploding headache, migraine-like headache, chronic tension headache, and
chronic thunderclap headache [10, 11]. In this study, we
analyzed the clinical characteristics of CVT patients with
or without headache and identified the risk factors for
headache in this population. Our findings may provide
guidance for the early diagnosis of headache in patients
with CVT.

Methods
Study design
A total of 69 consecutive patients who were diagnosed
with CVT between September 2017 and September
2019 in the First Affiliated Hospital of Soochow Univer-
sity were recruited. The inclusion criteria were as fol-
 lows: 1) patients who were diagnosed with CVT based
on clinical presentation and imaging examinations includ-
ing magnetic resonance venography (MRV), computed
tomographic venography (CTV), or conventional digital
subtraction angiography (DSA). In CTV, MRV, and DSA,
CVT patients showed filling defects in cerebral venous
sinuses. 2) patients were admitted to Neurology clinic.
3) patients were conscious, cooperative, and able to
provide all necessary information. Patients were excluded if
1) they were diagnosed without imaging examinations; 2)
they had arterial systemic cranial vascular disease, head
trauma, acute intracranial infection, renal or hepatic fail-
ure, acute myocardial infarction, or hematological malign-
nancy; 3) they were unwilling to cooperate or unable to
provide reliable information.

The patients were divided into two groups, the head-
ache group and the non-headache group, according to
the presence or absence of new-onset headache symp-
toms at admission. Headache was defined as a pain
on the top of the head, in the forehead, or an occipital
ache. Patients in each group were further classified
into three subgroups based on the stage of CVT: 1)
acute stage: ≤ 48 h; 2) subacute stage: between 48 h and
30 days; 3) chronic stage: ≥ 30 days [12]. All participants
received formal anticoagulation therapy. Patients with
severer CVT also received intravascular treatment. This
study was approved by the ethics committee of the hos-
pital. All patients provided written informed consent
(Fig. 1).

Data collection
The demographic and clinical data of 69 CVT patients
were collected and retrospectively reviewed. The char-
acteristics of patients with or without headache were
compared, including demographic features, date of
symptom onset, all symptoms presented from the
onset of the headache at admission, the results from
imaging examinations, and the National Institutes of
Health Stroke Score (NIHSS) at admission and at dis-
charge, Patient outcomes were assessed at discharge by
NIHSS. The following parameters, which were meas-
ured within 24 h after admission.The patients systolic
blood pressure(SBP), diastolic blood pressure(DBP)
were measured and analyzed in 24 h after admission.
Amount of thromboembolic cerebral venous sinus were
measured after having a MRV check. levels of D-dimer and
hypersensitive C-reactive protein, white blood cell count,
the number of lymphocytes(L), lymphocytes ratio(LR),
Mean corpuscular volume (MCV), levels of hepatitis
B surface antibody and blood urea nitrogen(BUN) in
peripheral blood in 24 h after admission. the pressure
of the cerebrospinal fluid (CSF), levels of protein, Lactic
dehydrogenase(LDH), and adenosine deaminase(ADA)in
the CSF were analyzed after undergoing a lumbar punc-
ture in 48 h after admission. Urine specific gravity (USG)
was detected in 24 h after admission, Patient outcomes
were assessed by two professional Physician of neurology
at discharge by NIHSS. The severity of CVT was deter-
mined by amount of thromboembolic cerebral venous
sinus. The severity of headache was evaluated using Vis-
ual Analogue Scale-100(VAS-100). An ICP of more than
200 mmH2O was defined as intracranial hypertension.

Statistical analysis
All data analyses were performed by SPSS (version 21,
IBM). Quantitative variables that were normally dis-
tributed were expressed as mean ± standard deviation,
whereas non-normally distributed data were shown as
median with inter-quartile range (IQR). Categorical
variables were presented as number and percentage (%).
Student’s *t*-test or Mann–Whitney test was used for the analysis of continuous data, while χ² or Fisher’s exact test was used to compare categorical data. The independent variables associated with headache and the risk factors for CVT were analyzed by logistic regression analysis. A difference was considered significant if *P* < 0.05.

**Results**

The overall incidence of headache was 75% (52/69) in this cohort. In the headache group (*n* = 52), 55.8% (29/52) of the patients were females. The median age was 37 years [IQR 27–45 years]. Among these patients, 28 (51.9%) had exploding headache; 15 (28.8%) had migraine-like headache; 3 (5.7%) had chronic tension headache; 6 (11.5%) had other types of headache. In the non-headache group (*n* = 17), 5 (29%) of the patients were females. The median age of patients without headache was 50 years [IQR 38–67 years] (Table 1).

Among all CVT patients, 47.82% of them were at the acute stage; 33.33% were at the subacute stage; and 18.84% were at the chronic stage. The proportions of headache patients at acute, subacute, and chronic stages were 53.84% (28/52), 28.84% (15/52), and 17.30% (15/52), respectively. In the non-headache group, the percentage of patients at acute, subacute, and chronic stages were 64.70% (11/17), 29.41% (5/17), 9% (1/11), respectively.

Head and face infection or upper respiratory infection occurred in 27.68% (26/91) of all CVT patients. There was no significant difference in the NHISS between headache and non-headache groups (0.0 [0.0, 1.00] vs. 0.5 [0.0, 1.75], *P* = 0.072). Among all participants, 67 of them received anticoagulant therapy (low molecular heparin,
5000 IU, subcutaneous injection, b.i.d.) for two weeks. Two patients received intravascular treatment. At discharge, 92.75% of all patients had an NIHSS of 0, indicating that they were in relatively good condition; 7.25% of them were in a relatively poor condition (NHISS > 1); 4 patients were in coma. One patient from the head group died during hospitalization (Table 1). The result of VAS-100 in patients with headache was 70.12 ± 13.8.

Compared with the non-headache group, patients with headache had lower median age (37 [27, 45] vs. 50 [38, 67], P = 0.004), MCV (88.10 [84, 91] vs. 90.4 [88.65, 92.40], P = 0.035), levels of BUN (3.5 [2.80, 4.15] vs. 4.75 [3.90, 6.00], P = 0.002), protein (CSF) (0.55 [0.284, 0.605] vs. 0.605 [0.605, 0.995], P = 0.002), LDH (CSF) (28 [22, 54] vs. 50 [34, 54], P = 0.045), and higher LR (0.25 [0.17, 0.32] vs. 0.17 [0.14, 0.24], P = 0.038) and ICP (234 [200, 290] vs. 200 [171.25, 234], P = 0.025). However, there was no significant difference in NHISS, ATCVS, DBP, WBC, L, USG, level of ADA (CSF), and treatment method between the two groups. The headache group had better outcomes at discharge (X^2 = 9.393, P = 0.024) (Table 1, Fig. 2).

The Spearman’s correlation analysis showed that the younger age (r = -0.352, P = 0.003), gender of female (r = 0.272, P = 0.026), increased LR (r = 0.252, P = 0.037) and ICP (r = 0.271, p = 0.024) were positively correlated with the occurrence of headache, whereas decreased MCV (r = -0.256, P = 0.034), lower levels of BUN (r = -0.370, P = 0.002) and protein (CSF) (r = -0.376, P = 0.001) were negatively correlated with the onset of headache in CVT patients (Table 2).

We further performed binary logistic regression analysis to identify the risk factors for headache in CVT patients. The occurrence of headache was defined as

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**Table 1** Demographic and clinical characteristics of patients at admission

|                          | Headaches groups n = 52 | Non-headaches groups n = 17 | X^2/Z-value | P-value |
|--------------------------|-------------------------|----------------------------|-------------|---------|
| Gender (male/female)     | 23/29                   | 12/5                       | 4.947       | 0.025   |
| Age (years)              | 37 (27, 45)             | 50 (38, 67)                | -2.862      | 0.004   |
| Subgroups                |                         |                            |             |         |
| Acute stage              | 28 (53.84%)             | 11 (64.70%)                | 1.423       | 0.0491  |
| Subacute stage           | 15 (28.85%)             | 5 (29.41%)                 |             |         |
| Chronic stage            | 9 (17.31%)              | 1 (9.09%)                  |             |         |
| ATCVS                    | 3 (1, 4)                | 3 (1, 3)                   | -0.732      | 0.670   |
| SBP (mmHg)               | 121 (112, 131)          | 129 (120, 141)             | -1.928      | 0.054   |
| DBP (mmHg)               | 74 (67, 80)             | 78.5 (69, 89.75)           | -1.132      | 0.258   |
| WBC (x 10^3/L)           | 7.33 (5.78, 8.92)       | 8.05 (6.49, 11.06)         | -1.436      | 0.151   |
| L (x 10^3/L)             | 1.7 (1.09, 2.08)        | 1.39 (1.05, 2.24)          | -0.555      | 0.579   |
| LR (%)                   | 0.25 (0.172, 0.327)     | 0.18 (0.14, 0.236)         | -2.076      | 0.038   |
| MCV (ng/L)               | 88.10 (84, 91)          | 90.4 (88.65, 92.40)        | -2.112      | 0.035   |
| USG                      | 1.014 (1.010, 1.020)    | 1.013 (1.010, 1.015)       | -0.993      | 0.479   |
| HBs-Ab (ug/ml)           | 24.03 (24.03, 154.54)   | 28.07 (59.75, 154.56)      | -0.271      | 0.787   |
| BUN (mg/L)               | 3.5 (2.80, 4.15)        | 4.75 (3.90, 6.00)          | -3.052      | 0.002   |
| ICP (mm H2O)             | 234 (200, 290)          | 200 (171.25, 234)          | -2.237      | 0.025   |
| Protein (CSF) (g/L)      | 0.55 (0.284, 0.605)     | 0.605 (0.605, 0.995)       | -3.103      | 0.002   |
| ADA (CSF) (U/L)          | 0.4 (0.20, 0.73)        | 0.73 (0.40, 0.73)          | -1.638      | 0.101   |
| LDH (CSF) (U/L)          | 28 (22, 54)             | 50 (34, 54)                | -2.004      | 0.045   |
| CL (CSF) (mmol/L)        | 121.50 (120, 70, 125.30)| 120.70 (120, 70, 123.67)   | -1.384      | 0.166   |
| NHISS (at discharge)     | 0.00 (0, 1)             | 0.5 (0, 1.75)              | -1.798      | 0.072   |
| Treatment method         |                         |                            |             |         |
| Low molecular heparin    | 50 (96.15%)             | 17 (100%)                  | 0.673       | 0.412   |
| Intravascular treatment  | 2 (3.84%)               | 0 (0)                      |             |         |
| Prognosis                |                         |                            |             |         |
| Improved                 | 50 (96.15%)             | 14 (82.35%)                | 9.393       | 0.024   |
| Exacerbation/complications| 1 (1.92%)               | 3 (17.65%)                 |             |         |
| Death                    | 1 (1.92%)               | 0 (0)                      |             |         |

ATCVS: Amount of thromboembolic cerebral venous sinus, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, WBC: White blood cell count (x 10^9/L), LR: Lymphocyte ratio, MCV: Mean corpuscular volume, USG: Urine specific gravity, HBs-Ab: Hepatitis B surface antibody, BUN: Blood urea nitrogen, ICP: Intracranial pressure, CSF: Cerebrospinal fluid, ADA: Adenosine deaminase, LDH: Lactic dehydrogenase, NHISS: The National Institutes of Health Stroke Scale, LWMMH: Low molecular heparin
Fig. 2 The comparison of clinical characteristics of patients at admission between two groups (head-group & non-headgroup). a, the age ($p = 0.004$), b, the MCV ($p = 0.035$), c, LR ($p = 0.038$), d, the BUN ($p = 0.002$), e, the ICP ($p = 0.025$), f, protein(CSF) ($p = 0.002$), g, LDH(CSF) ($p = 0.045$). LR: Lymphocyte ratio, MCV: Mean corpuscular volume, BUN: Blood urea nitrogen, ICP: Intracranial pressure, CSF: Cerebrospinal fluid, LDH: Lactic dehydrogenase. ($p \leq 0.05$ means significantly difference)
a dependent variable and the independent variables included DBP, SBP, NHISS, WBC, L, LR, MCV, USG, ICP, levels of HBs-Ab, BUN, protein (CSF), ADA (CSF), LDH (CSF), CI− (CSF), and NHISS (at discharge). The results showed that younger age (adjusted odds ratio (OR) = 0.912, 95% confidence interval (CI): 0.840–0.990, \( P = 0.029 \)) and the increased level of CI− (CSF) (adjusted OR = 1.742, 95% CI: 1.037–2.927, \( P = 0.036 \)) were the predictive factors for the occurrence of headache in CVT patients (Table 3).

We found the amount(percentage) of thromboembolic cerebral venous sinus were sigmoid sinus 27(20.7%), transverse sinus 50(38.4%), superior sagittal sinus 19(14.6%), inferior sagittal sinus 6(4.6%), torcular herophili 11(8.4%), straight sinus 17 (13.1%) in the headache group patients, and sigmoid sinus 11(33.4%), transverse sinus11(33.4%), superior sagittal sinus 4(12.1%), inferior sagittal sinus 1(3.0%), torcular herophili 3 (9.0%), straight sinus 3(9.0%) in the non-headache group patients (Fig. 3).

**Discussion**

Headache is one of the most common symptoms in CVT patients. In this cohort, 75% (52/69) of the patients reported headache at admission, which was consistent with a previous study showing that 80–90% of CVT patients presented with headache [13]. Previous evidence reveals that CVT is most prevalent among young women [14]. Here, we found that patients with headache were younger than those in the non-headache group. Also, 78.7% of our patients were females. It has been reported that headache is associated with papilledema in 25–75% of CVT patients [15]. The proportions of female patients in headache and non-headache groups were 55.67% and 29.42%, respectively. Headache may occur at the acute, subacute, or chronic stages of CVT. Botta et al. found that headache onset was acute in 51.1%, subacute in 42.6%, thunderclap in 4.3%, and chronic in 2.1% of the CVT patients and the mean VAS was 76.4±18.8 [10], which was consistent with our findings.

Infection has been considered as one of the most common causes of CVT [16] and the neutrophil-to-lymphocyte ratio is significantly associated with poor outcomes at discharge [16, 17]. Our study showed that head and face infection or upper respiratory infection occurred in 27.68% (26/69) of the patients. Compared

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**Table 2** Correlations between demographic/clinical characteristics and the occurrence of headache in CVT patients

| r-value | P-value |
|---------|---------|
| Age (years) | 0.352 | 0.003 |
| Gender | 0.272 | 0.026 |
| LR(%) | 0.252 | 0.037 |
| ICP (mg/L) | 0.271 | 0.024 |
| BUN (mg/L) | -0.370 | 0.002 |
| MCV(mg/L) | -0.256 | 0.034 |
| Protein (CSF) (g/L) | -0.376 | 0.001 |

LR Lymphocyte ratio, MCV Mean corpuscular Volume, BUN Blood urea nitrogen, ICP Intracranial pressure, CSF Cerebrospinal fluid, r Relation coefficient

**Table 3** Binary logistic regression analysis

| B     | S.E  | Walds | p-value | Exp (B) | EXP(B) 95% C.I |
|-------|------|-------|---------|---------|----------------|
| Gender | 1.775 | 1.756 | 1.022   | 0.312   | 5.902          |
| Age(years) | -0.092 | 0.042 | 4.789   | 0.029   | 0.912          |
| SBP (mmHg) | -0.104 | 0.056 | 3.442   | 0.006   | 0.901          |
| DBP (mmHg) | 0.078 | 0.055 | 2.063   | 0.151   | 1.082          |
| NHISS | -0.155 | 0.219 | 0.499   | 0.480   | 0.857          |
| WBC(× 10^9/L) | 0.282 | 0.312 | 0.819   | 0.365   | 1.326          |
| PLT(× 10^12/L) | -0.010 | 0.007 | 2.132   | 0.144   | 0.990          |
| ATCVS | 0.046 | 0.465 | 0.010   | 0.922   | 1.047          |
| ICP(mg/L) | 0.015 | 0.011 | 2.130   | 0.144   | 1.016          |
| CL− (CSF) (mmol/L) | 0.555 | 0.265 | 4.393   | 0.036   | 1.742          |
| LDH(CSF) (U/L) | -0.006 | 0.111 | 2.58    | 0.612   | 0.994          |
| BUN(mg/L) | -0.101 | 0.538 | 0.035   | 0.851   | 0.904          |
| L(× 10^9/L) | -1.929 | 1.779 | 1.176   | 0.278   | 0.145          |
| PT(second) | 0.163 | 0.303 | 0.289   | 0.591   | 1.177          |
| Fibrinogen(g/L) | -0.130 | 0.428 | 0.093   | 0.761   | 0.878          |

SBP Systolic blood pressure, DBP Diastolic blood pressure, NHISS the National Institutes of Health Stroke Scale, WBC (× 10^9/L) White blood cell count, PLT Blood platelet, ATCVS Amount of thromboembolic cerebral venous sinus, ICP Intracranial pressure, CSF Cerebrospinal fluid, LDH Lactic dehydrogenase BUN Blood urea nitrogen, L Lymphocyte, PT Prothrombin time
to the non-headache group, patients with headache had a higher LR. However, no significant difference was observed in other inflammation markers, such as WBC and the number of lymphocytes. We also found that a high level of HBs-Ab in all CVT patients, but there was no significant difference between the headache and non-headache groups. Previous studies reported that CVT patients had a higher HBs-Ag-positive rate compared to health controls [16, 18], indicating HBV infection may be a risk factor for CVT [18].

Intracranial CSF pressure is an important sign of CVT [1, 19]. In the current study, the ICP exceeded 200 mm H₂O in both groups. Also, CVT patients with headache showed higher ICP compared to the non-headache group. Intracranial hypertension caused indirectly by a mass compressing part of the intracranial venous sinuses, resulting in obstruction of venous drainage [17].

CSF examination provides important information for the diagnosis of CVT. Most CVT patients have normal or increased cell counts and protein concentrations in the CSF [1]. In our cohort, the headache group showed significantly lower levels of protein (CSF), Cerebrospinal fluid protein content is increased in all patients with cerebral venous sinus thrombosis. Compared with non-headache patients, cerebrospinal fluid protein content is relatively lower in headache patients, which may be related to increased protein catabolism or poor nutrition in headache patients. ADA (CSF), LDH (CSF), and CI-(CSF) also were lower compared to patients non-headache. The changes in CSF profile in headache patients may be related to the inflammation of sensory nerves. We also demonstrated that the MCV in the headache group was significantly lower than that in patients without headache. Anemia caused by iron deficiency is a common disorder in juvenile populations [20]. Iron-deficiency anemia has been identified as a contributor to the development of CVT [21]. Some patients have normal hemoglobin, and although the MCV is lower, we have found that red blood cells are small and prone to suffer CVT. Hypercoagulability and venous stasis have also been shown to play vital roles in the pathogenesis of thrombus [4]. Further investigations are needed to explore the relationships between these clinical parameters and headache in CVT patients.

There are some limitations in this study. First, due to the low incidence of CVT. The number of recruited

![Fig. 3 Differences of ATCVS, amount of thromboembolic cerebral venous sinus (diseased sinus) between two groups (head-group & non-headgroup) were significant. The figure shown sigmoid sinus 27(20.7%), transverse sinus 50(38.4%), superior sagittal sinus 19(14.6%), inferior sagittal sinus 6(4.6%), torcular herophili 11(8.4%), straight sinus 17(13.1%) in the headache group patients, and sigmoid sinus 11(33.4%), transverse sinus 11(33.4%), superior sagittal sinus 4(12.1%), inferior sagittal sinus 1(3.0%), torcular herophili 3(9.0%), straight sinus 3(9.0%) in the non-headache group patients ($p \leq 0.05$ means significantly difference)
The age, LR, MCV, levels of BUN, ICP, protein (CSF), and LDH (CSF) in headache patients were significantly different from those in the non-headache group. Younger age and a lower level of CI- (CSF) were risk factors for the occurrence of headache in CVT patients. These findings may provide guidance for clinical diagnosis and treatment of CVT.

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**Authors’ contributions**

Yugang Wang, Xiaozhu Shen, Ping Wang acquired the data, analyzed he results, and wrote the main manuscript text and Qi Fang guided the process, interpreted the results, and revised the article. All authors read and approved the manuscript.

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**Availability of data and materials**

The datasets generated and/or analysed during the current study are not publicly available due to containing private information such as age and gender but are available from the corresponding author on reasonable request.

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the Ethical Committee of the First Affiliated Hospital of Soochow University. All patients signed an informed consent approved by the review board. Research involving human participants, human material, or human data, must have been performed in accordance with the Declaration of Helsinki. All procedures carried out in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee (No.2022–106).

**Consent for publication**

All authors consented the work to be published, This study does not include identifying information/images, we declared that the consent for publication was not applicable.

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