Anatomic Asymmetry of Transverse Sinus May Be Irrelevant to the Prognosis of Intracerebral Hemorrhage

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Background: We investigate the probable effect of anatomic asymmetry of transverse sinus (TS) on the outcomes of acute intracerebral hemorrhage (ICH), to provide reference for customized treatment.

Methods: Consecutive patients with imaging-confirmed acute ICH were enrolled from October 2015 through October 2019, and divided into 2 groups: symmetrical and unilateral (left or right) slender TS groups, based on the status of TS in imaging maps. Brain computed tomography (CT) maps of all patients at baseline and half-month post-ICH were obtained, and the volumes of hematoma and the perihematomal edemas (PHE), as well as the modified Rankin Scale (mRS) scores at the month-3 post-ICH between the 2 groups were assessed and analyzed.

Results: A total of 46 eligible patients entered into final analysis, including 18 cases in the slender TS group (14 cases involved the left side while 4 cases involved the right side), and 28 cases in the symmetrical TS group. The mRS scores, hematoma absorption rates, and the residual volumes of PHE of all patients in the 2 groups at half-month post-ICH showed no statistical significance (all $P > 0.05$), and all of the items mentioned above were related to the hematoma volume at baseline (all $P < 0.001$). At the month-3 follow-up post-ICH, the mRS scores between the 2 groups showed no statistical significance as well ($P = 0.551$).

Conclusions: Anatomic asymmetry of TS may not affect the prognosis of PHE and clinical outcome after ICH.

Key Words: slender, transverse sinus, cerebral hemorrhage, brain edema

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Brain edema surrounding the hematoma after spontaneous intracerebral hemorrhage (ICH) was well-recognized as one of the key factors associated with secondary brain injury post-ICH.[1] The underlying mechanisms may include vasogenic and cytotoxic edema that caused by ischemia and hypoxia, inflammatory reactions, and blood-brain barrier (BBB) destruction.[2,3] Previous studies revealed that the volume of perihematomal edema (PHE) closely related to poor outcomes of ICH.[2] Intensive control of PHE may inhibit further deterioration of neurological dysfunction after ICH.

Current evidence indicated that many factors could affect the severity of PHE after ICH, such as the hematoma size, diabetes mellitus and aging, etc.[4–7] However, it is still unclear whether the anatomic asymmetry of transverse sinuses (TS), considered as normal variant, can affect the volume of PHE and clinical outcomes in patients with ICH is still unclear.

Our previous studies revealed that both thrombotic and non-thrombotic TS stenosis were able to result in severe cerebral hypertension, and often manifested as decreased arterial perfusion throughout the brain.[8,9] Increasing evidence suggested that TS asymmetry, especially the occlusion of the ipsilateral cranial venous drainage, could negatively affect the early fatal edema and clinical course in patients with middle cerebral artery infarction.[10–13]

A recent study suggested that insufficient ipsilateral cortical venous drainage might worsen the early formation of PHE after cerebral hemorrhage[14]; however, it remained undetermined whether the slenderness of TS, a main pathway for cerebral venous outflow, could interfere the ICH-related cerebral edema or not. Herein, we aimed to determine the effect of anatomic slender TS imposed on ICH-induced PHE.

METHODS

Participants

Patients with both acute ICH and ipsilateral slender TS or symmetrical TS, confirmed by computed tomography venography (CTV) or magnetic resonance venography (MRV) were consecutively enrolled into this study from January 2015 through October 2019. Their clinical and imaging data were obtained from our inpatient database, and 2 neurologists along with 2 experienced radiologists strictly reviewed and analyzed their data in double-blind manner.

Inclusion criteria: (1) acute primary ICH within 1 day as confirmed by CT; (2) slender TS or symmetrical TS as identified by CTV or MRV; (3) no sex or age limitation.

Exclusion criteria: (1) secondary ICH that caused by trauma, aneurysm, arteriovenous malformation, venous thrombosis, hemorrhagic transformation owing to cerebral infarction, or isolated intraventricular hemorrhage, etc.; (2) high intracranial pressure before the onset of ICH symptoms; (3) the history of cerebrospinal fluid shunt; (4) cerebral venous sinus thrombosis or internal jugular venous thrombosis; (5) incomplete clinical or imaging data.

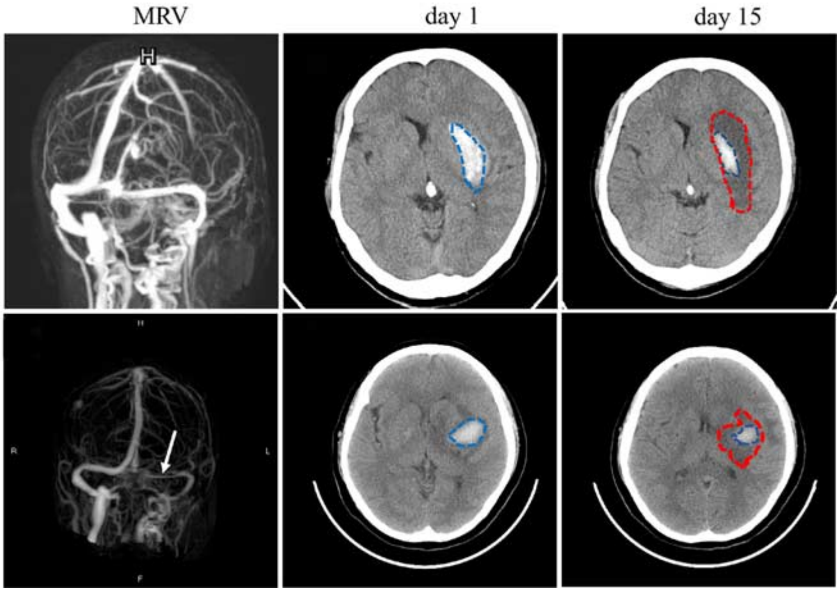

FIGURE 1. Region of interest analyses. Hematoma (blue) and visible perihematoma edema (red) volumes shrank on both noncontrast computed tomography and CT perfusion sequences. Ventricles were excluded. White arrow pointed to the slender transverse sinus on the left side. MRV indicates magnetic resonance venography; TS, transverse sinus.

Clinical items, including age, sex, National Institute of Health Stroke Scale (NIHSS), and the concomitant diseases (such as: hypertension, diabetes), and the usage of antiplatelet and warfarin at admission were collected and analyzed. Laboratory data included white blood cell count, platelet count, prothrombin time, low-density lipoprotein, high-density lipoprotein, uric acid, and homocysteine levels.

Registration and Informed Consents

The Ethic Committees of both Xuanwu Hospital Capital Medical University and the Affiliated Hospital of Jiujiang University approved the study. All clinical studies were conducted in accordance with the principles of the Declaration of Helsinki. All patients signed the informed consent forms before their enrollment.

Edema Volume Evaluation

CTV and CT maps of all patients enrolled were analyzed by the picture archiving and communication system. The hematoma volumes (excluding ventricular hemorrhage) at baseline and follow-up CT imaging maps were measured manually by 2 investigators independently, who blinded to the clinical data. The examiner manually drew regions of interest (ROIs) by tracing the hyper-dense area (hematoma) and hypo-dense region surrounding the hematoma (PHE).[15] Threshold ranges for hematomas and edemas were 44 to 100 and 5 to 33 HU, respectively. The computer automatically added up the area of each floor to create the final volume. Similarly, the volume of total lesions (hyper-dense + hypo-dense) was calculated. The PHE volume was measured by subtracting the hematoma volume from the volume of total lesions (Figs. 1B, C).

TS Evaluation

To minimize linear filling defects, TS caliber was measured in mm on 3D MIP reconstruction at the mid-lateral portion of the TS. TS was considered asymmetric if the side-to-side diameter differed by $>10\%$.[8,16] TS morphology was graded as follows: *symmetric TS* included the symmetry TS and those with $\leq 10\%$ asymmetry TS compared with the contralateral; *asymmetric TS* represented the asymmetry TS $>10\%$ compared with the contralateral. The asymmetry TS was further graded as moderate (10% to 50%) or severe ($>50\%$) compared with the contralateral; *aplastic TS* indicated an absence of the TS signal in MRV maps (Fig. 2).

Based on the 3-dimensional reconstructed sequences of CTV or MRV maps, a slender TS was defined as the slim TS involving a long segment (more than 2 cm) and the diameter <50% of the opposite without abnormal collateral veins simultaneously.

Neurological Functional Outcomes

The modified Rankin Scale (mRS) was used to evaluate neurological function at month-3 post-ICH of all patients, and evaluated by 2 physicians, who had no access to our study protocol, in their outpatient clinic follow up. The mRS scores of 0 to 2 and 3 to 6 were defined as good and poor outcomes, respectively.

Statistical Analysis

The Social Science Statistical Software Package (SPSS) 22.0 was used for data analysis. Continuous variables were represented by average values. The Fisher exact test or Ka test was used to compare categorical variables, 2-sample independent *t* test was used to compare continuous variables, and multiple linear regression was used to compare outcomes and multivariate variables. Binary logistic regression was used to analyze the mRS results and variables. Differences were considered statistically significant at 2-sided *P*-values <0.05.

RESULTS

Demographic Characteristics

A simplified flow chart for cases selection was showed in Figure 3. A total of 46 patients, including 18 cases in slender TS group (female/male = 11/7, median 52 ± 3 y) and 28 cases in symmetrical TS group (female/male = 12/16, median 58 ± 2 y), were enrolled into the final analysis. The baseline average NIHSS scores at admission were 7 ± 2, and the median time

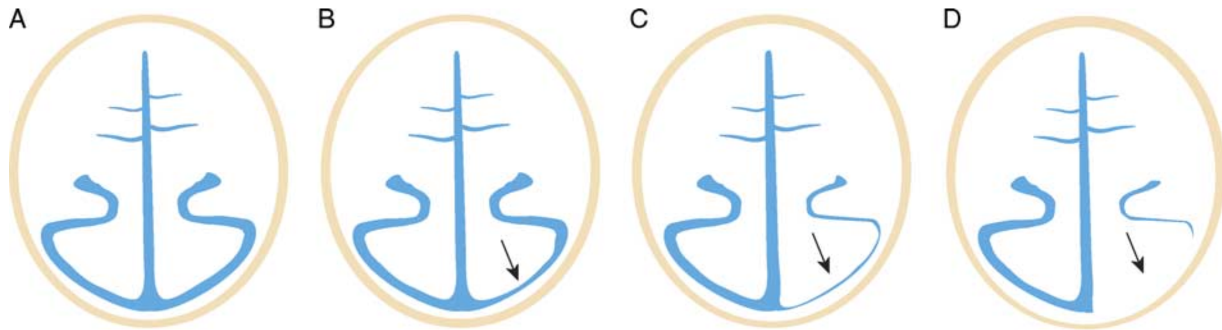

FIGURE 2. Schematic diagram of transverse sinus: (A) symmetrical transverse sinus; (B) moderate slender transverse sinus (arrow); (C) severe slender transverse sinus (arrow); (D) asymmetry transverse sinus aplasia (arrow).

from ICH onset to the CTV or MRV scan was 1 day. The prevalence of hypertension and diabetes was proportionately balanced between the 2 groups (both $P > 0.05$). All of the hematoma located at the territory of anterior circulation, and the incidence of the hematoma broken into cerebral ventricle accounted for 6.5% (3/46). In which, only one patient had a history of oral antiplatelet drug before ICH (Table 1).

Slender TS in Patients With ICH

All qualified patients were identified with normal superior sagittal sinuses, in which, 28 cases had symmetrical TS, whereas 18 cases had unilateral slender TS (including 14 cases in left and 4 cases in right). Among them, 6 cases with left slender TS were with ipsilateral ICH, others were with ICH located at the contralateral hemisphere of the slender TS.

Clinical Outcomes Post-ICH

Table 1 displayed neurological dysfunction post-ICH in patients with or without slender TS. Univariate analysis revealed that the slender TS had no relationship with the month-3 clinical outcomes ($P = 0.551$). Binary logistic regression analysis showed that after adjusting the factors of age, baseline NIHSS, hypertension, diabetes, low-density lipoprotein, high-density lipoprotein, uric acid, etc., both the volumes of hematoma at baseline and the volumes of residual edema at the half-month post-ICH were independently associated with the poor clinical outcomes at month-3 ($P = 0.038$).

Left Slender TS May not Slow Ipsilateral PHE Absorption

In order to investigate whether the slender TS affects ipsilateral PHE absorption. We conducted subgroup analysis. Twenty-three cases with left ICH, including 6 cases of left slender TS and 17 cases of symmetric TS. The baseline volume of hematoma and NIHSS scores between left slender TS and symmetric TS were: 6.33 ± 2.51 mL versus 12.7 ± 4.60 mL, and 2.67 ± 1.09 versus 7.53 ± 2.00, respectively, all $P > 0.05$. The PHE volumes at half-month post-ICH between the 2 groups were 29.53 ± 13.41 mL

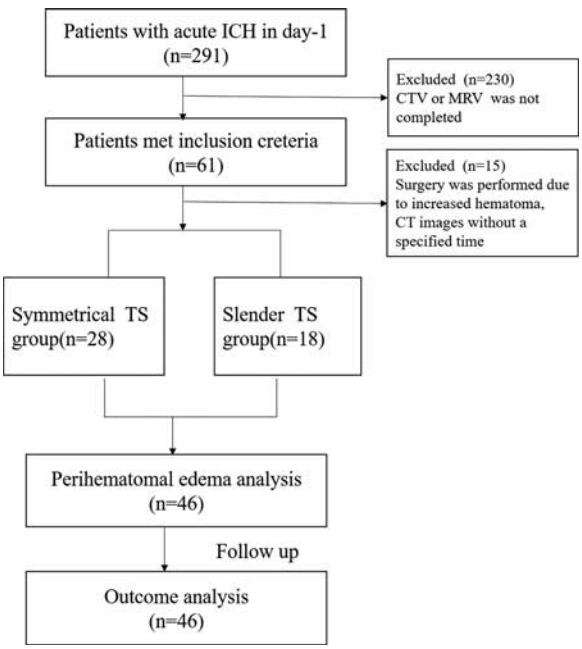

FIGURE 3. Inclusion and exclusion flow diagram. CT indicates computed tomography; CTV, computed tomography venography; ICH, intracerebral hemorrhage; MRV, magnetic resonance venography; TS, transverse sinus.

TABLE 1. Characteristics of the Patients With ICH

Items	ICH With Slender TS, N = 18	ICH With Symmetrical TS, N = 28	*P*
Demographics, n (%)			
Female	11 (61)	12 (42)	0.236
Age, mean ± SD (y)	52 ± 3	58 ± 2	0.124
Hypertension	12 (67)	19 (68)	0.935
Diabetes mellitus	3 (16)	2 (7)	0.322
Antiplatelet treatment	2 (11)	0 (0)	0.074
Warfarin use	0	2 (7)	0.256
History of smoking	12 (66)	13 (46)	0.179
Baseline NIHSS score, mean ± SD	7 ± 2	7 ± 2	0.800
Baseline hematoma volume, mean ± SD (mL)	15.05 ± 5.19	13.78 ± 2.99	0.821
Follow-up, mean ± SD			
Hematoma Volume after half a month (mL)	4.87 ± 1.29	4.26 ± 1.18	0.751
PHE volume after half a month (mL)	34.92 ± 9.75	22.24 ± 8.18	0.330
mRS at month-3	0.67 ± 1.03	0.96 ± 1.04	0.551

ICH indicates intracerebral hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; PHE, perihematomal edemas; TS, transverse sinus.

TABLE 2. Comparison of Slender TS and Symmetric TS With Left Hemisphere ICH

Items	Left Slender TS, N = 6	Bilateral Symmetric TS, N = 17	*P*
Baseline NIHSS score	2.67 ± 1.09	7.53 ± 2.00	0.932
Baseline hematoma volume (mL)	6.33 ± 2.51	12.7 ± 4.60	0.435
Follow-up hematoma volume (mL)	3.26 ± 1.8	3.83 ± 1.63	0.850
PHE volume at half-Month post-ICH (mL)	29.53 ± 13.41	25.68 ± 13.30	0.874
mRS at month-3	0.17 ± 0.41	1.12 ± 1.11	0.056

ICH indicates intracerebral hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; PHE, perihematomal edemas; TS, transverse sinus.

versus 25.68 ± 13.30 mL ($P > 0.05$); and the mRS between the 2 groups at month-3 were 0.17 ± 0.41 versus 1.12 ± 1.11, $P > 0.05$ (Table 2).

DISCUSSION

The peak of PHE usually appeared at the week-2 post-ICH, which might relate to the outcomes of ICH. Besides the factors of hematoma size, diabetes mellitus and aging that considered to be the determinators of the severity of PHE,[2,4–7] our study failed to find the effect of the slender TS on the PHE and the 3-month mRS after ICH, despite previous studies showed that the slender TS might affect the edema volume after cerebral infarction.[12,13]

As we all know that the intracranial venous system was responsible for the dynamics of cerebral venous blood and cerebrospinal fluid, which played an important role in maintaining cerebral arterial perfusion and intracranial pressure. According to previous research, 30% to 41% of healthy adults were imaged with an asymmetric slender lateral sinuses and sigmoid sinuses, whereby the slender TS was often considered as anatomic variation[14] which was in accordance with our findings that 18 of 46 patients (39.13%) in this study were found with unilateral slender TS. We defined the slender TS in this study as follows: one side long-segment of slender TS showed in CTV or MRV and no abnormal collateral veins surrounded, simultaneously. Meanwhile, the patients had no symptoms of headache or tinnitus before ICH onset.

Herein, we only discussed whether the asymmetric slender TS could affect the outcomes of ICH. On the contrary, symptomatic cerebral venous sinus stenosis, another disease entity, which often presented with increased intracranial pressure, repeated headaches, nausea and tinnitus, combined with localized venous sinus stenosis and abnormal expanded collaterals on CTV or MRV maps, was rejected in this study.[9]

Slender TS May Not Affect the Prognosis of PHE

In this study, the volumes of PHE in both slender and symmetric TS groups were compared at half-month post-ICH, the average volumes of PHE were 34.92 ± 9.75 mL in the slender TS group and 22.24 ± 8.18 mL in the symmetric TS group, respectively, which showed no statistical significance, regardless of whether the hematoma located on the ipsilateral or contralateral side of the slender TS. If the imaging and hemodynamics of the cerebral venous and sinus systems can be carefully evaluated in the future, more evidence will be obtained.

However, Chen and colleagues' study showed that poor venous drainage in ipsilateral cortex might affect PHE after early cerebral hemorrhage, herein, researchers reconstructed the original CTA image at the first 6-hours post-ICH and found that the void outflow signal in ipsilateral cortical veins appeared in about one-third of patients, which might be closely related to the aggravation of PHE.[17] Whereas, that study neither reconstructed the venous sinus image nor investigated whether slender TS affected the development of PHE. Considering that the peak of PHE was about 2 weeks, we only observed the volumes of residual PHE and hematoma in half a month post-ICH.

Our study for the first time revealed that slender TS had no obvious effect on the outcomes of PHE and hematoma post-ICH. Whereby, additional intervention to the slender TS may be not necessary in these patients.

Slender TS May not Affect the Clinical Outcome After ICH

The factors, which might affect the 3-month mRS scores post-ICH, were analyzed using binary logistic regression, a statistical significance between hematoma volume and white blood cell count was noticed, rather than the slender TS. Our results suggested that slender TS did not relate to the month-3 mRS post-ICH (Fig. 4). Moreover, we noticed that the residual edema volume of PHE at half a month might not affect the month-3 mRS score in patients with either slender TS or symmetric TS post-ICH. In subgroup analysis, the group with slender left TS also did not affect absorption of ipsilateral PHE and did not result in a worse prognosis.

Previous study suggested that the peak volume of PHE was an independent predictor of the outcome in day 90 in patients post-ICH and was associated with age, hematoma

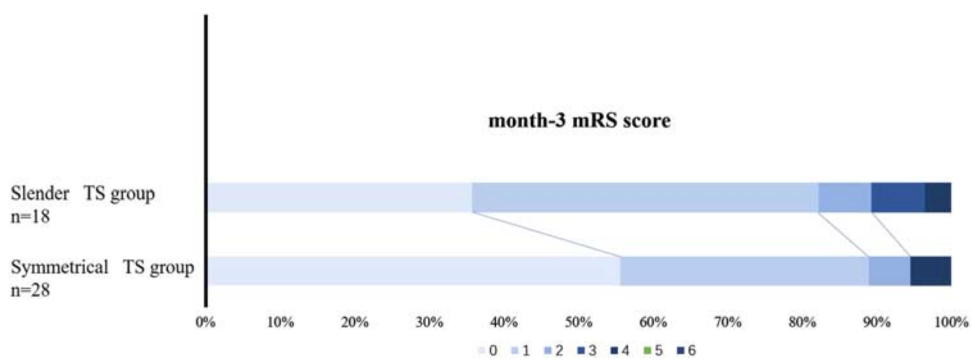

FIGURE 4. The mRS scores between slender and symmetrical venous sinus groups at month-3 post intracerebral hemorrhage. No remarkable differences were observed in either univariate or multivariate analyses. mRS indicates modified Rankin Scale; TS, transverse sinus.

volume, the initial 3 days of PHE increasing, and inflammation, each milliliter of additional peak volume of PHE increased the absolute risk for a poor outcome by 1.5%.[14]

Our study revealed that the outcomes of PHE showed no statistical difference between the slender TS group and the symmetric TS group, therefore, the clinical outcomes of ICH in the 2 groups might be less related to the slender TS. Moreover, the slender TS enrolled in this study was those with TS diameter <50% to the contralateral and length > 2 cm, which might be an agenesis, and the pathologic TS stenosis caused by various etiologies were excluded.[9,18–20]

Our previous study found that cerebral venous sinus stenosis was apt to be neglected and misdiagnosed owing to its nonspecific symptoms, which mainly comprised headache, tinnitus, head-noise, dizziness, eye swollen, and cerebral hypertension.[21] They are usually pathologic stenosis (blocked by giant arachnoid particles or sinus thrombi, etc.), presented with very short segment of local stenosis in imaging, and tinnitus or idiopathic intracranial hypertension in clinical setting, which were corrected by stenting and obtained good outcomes.[22] However, whether the pathologic TS stenosis can affect the prognosis of ICH is still unclear, and our future study is still on going.

Limitation

Several limitations in this study were worthy mentioned. First of all, the nature of a retrospective study with a small sample size is one of the most important issues. In addition, compared with previous study, patients in this study were with a lower ratio of hematoma expansion and the smaller hematoma volume. Moreover, we did not measure lumber puncture opening pressure to assess the intracranial pressure for its invasiveness.

CONCLUSION

Anatomic asymmetry of TS may not affect the prognosis of PE and clinical outcome post-ICH.

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