SHORT REPORT

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Previous chronic symptomatic and asymptomatic cerebral hemorrhage in patients with acute ischemic stroke

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Abstract

Purpose Identifying previous chronic cerebral hemorrhage (PCH), especially asymptomatic cases in patients with ischemic stroke, is essential for proper antithrombotic management. The study aimed to further clarify the prevalence of PCH and the associated factors in patients with acute ischemic stroke using multi-modal neuroimaging including susceptibility-weighted MR imaging (SWI).

Methods This was a retrospective cross-sectional study of 382 patients with acute ischemic stroke. All patients underwent 3.0-T MRI for cranial SWI, 1.5-T or 3.0-T conventional cranial MRI, and cranial CT. Patients found with PCH were matched 1:4 with patients without PCH. Clinical manifestation, computed tomography, conventional cranial MRI, and cranial SWI were used to determine PCH. Clinical and neuroimaging findings between the patients with symptomatic vs. asymptomatic PCH were compared.

Results Thirty-six patients (36/382, 9.4%) were determined to have had a PCH. Of these 36 patients, 17 (17/36, 47.2%, or 17/382, 4.5%) had asymptomatic PCH. Multivariable analysis showed that serum total cholesterol (OR = 0.510, 95%CI 0.312–0.832, $P = 0.007$), cerebral microbleeds (OR = 6.251, 95%CI 2.220–17.601, $P = 0.001$), and antithrombotic drugs history (OR = 3.213, 95%CI 1.018–10.145, $P = 0.047$) were independently associated with PCH. Asymptomatic PCH had similar clinical and neuroimaging characteristics with symptomatic PCH.

Conclusion PCH is not uncommon in acute ischemic stroke patients. Total serum cholesterol, cerebral microbleeds on SWI, and history of antithrombotic drugs were independently associated with PCH in patients with acute ischemic stroke. Asymptomatic PCH, which is easier to be missed and has similar characteristics with symptomatic PCH, should draw much attention.

Keywords Ischemic stroke · Susceptibility-weighted MR imaging · Previous chronic cerebral hemorrhage

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Introduction

Patients with cerebral hemorrhage frequently have indications for antithrombotic therapy. This represents a therapeutic dilemma as cerebral hemorrhage is considered a contraindication to antithrombotic medication. There were no long-term randomized studies addressing this issue. Some acute ischemic stroke patients may have had a previous chronic cerebral hemorrhage (PCH) that could recur with the use of antithrombotic therapy for secondary prevention, leading to poorer outcomes [1–7].

Susceptibility-weighted MR imaging (SWI) is more sensitive to fresh or chronic cerebral hemorrhagic lesions than conventional MRI and allows the detection of PCH, especially for asymptomatic one that was easily to be misdiagnosed [8]. Identifying PCH in patients with acute ischemic stroke could

be essential for prudent initiation of antithrombotic therapy, esp., intensive antithrombotic therapy. However, the prevalence of PCH and proper method to detect asymptomatic or symptomatic PCH needs to be further clarified for acute ischemic stroke patients. Therefore, this study used SWI examination, combined with multi-modal neuroimaging examinations and detailed clinical data, to observe the prevalence of PCH (symptomatic or not) and analyze the associated factors of PCH in patients admitted for acute ischemic stroke in a comprehensive stroke center.
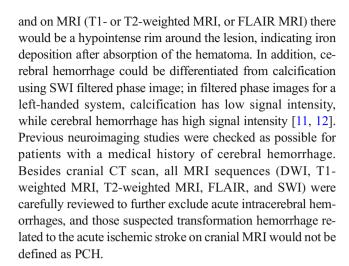
Methods

Patients

This retrospective cross-sectional study analyzed patients who were diagnosed with acute ischemic stroke and admitted at the stroke center of our hospital, one of national comprehensive stroke centers between 12/12/2011 and 3/6/2013. This study was approved by the ethic committee of our hospital. Informed consent was waived by the committee because of the retrospective nature of the study. The patient inclusion criteria are presented in the Supplemental Material.

Neuroimaging

All patients underwent CT in the emergency room to exclude acute cerebral hemorrhage. Conventional MRI and diffusion-weighted imaging (DWI) were completed within 5 days of admission. SWI was performed within 10 days of admission. Examinations were blindly reviewed by two experienced neurologists. A third senior physician was invited for consensus in case of controversy between the first two physicians. Details about the MRI examinations are provided in the Supplemental Material.

Cranial SWI were used to observe and analyze cerebral microbleeds (CMBs) [8, 9]. According to the Microbleed Anatomical Rating Scale (MARS) [10], CMB was defined as circular or oval low signal lesions with clear boundary on SWI sequence, with a diameter of 2–10 mm, while excluding lesions with similar imaging manifestations (including calcification, ferruginous sediment, cavernous hemangioma.) by combining with phase diagrams, mIP, other MRI sequences [11, 12], and cranial CT. The amount of CMBs was recorded according to the MARS for quantitative evaluation [10].

The presence of PCH was determined based on non-enhanced cranial CT, conventional cranial MRI scanning (routine scanning sequence), cranial SWI examination, and disease history. PCH referred to hypointensity on SWI magnitude images, with a diameter > 1 cm. They appeared as softened hypodense lesions on cranial CT, hypointensity on T1-weighted MRI, and hyperintensity on T2-weighted images,

and on MRI (T1- or T2-weighted MRI, or FLAIR MRI) there would be a hypointense rim around the lesion, indicating iron deposition after absorption of the hematoma. In addition, cerebral hemorrhage could be differentiated from calcification using SWI filtered phase image; in filtered phase images for a left-handed system, calcification has low signal intensity, while cerebral hemorrhage has high signal intensity [11, 12]. Previous neuroimaging studies were checked as possible for patients with a medical history of cerebral hemorrhage. Besides cranial CT scan, all MRI sequences (DWI, T1-weighted MRI, T2-weighted MRI, FLAIR, and SWI) were carefully reviewed to further exclude acute intracerebral hemorrhages, and those suspected transformation hemorrhage related to the acute ischemic stroke on cranial MRI would not be defined as PCH.

Classification of acute stroke

Stroke was classified according to the TOAST (Trial of org10172 in Acute Stroke Treatment) classification [13] and combined with disease history and imaging characteristics of the patients, and acute ischemic stroke was classified into five types: large-artery atherosclerosis (LAA), small-artery occlusion (SAA), cardiogenic embolism (CE), stroke of other demonstrated etiology (SOE), and stroke of other undemonstrated etiology (SUE). Hemorrhagic transformation during acute stroke was defined as the development of a hemorrhage after an acute ischemic stroke.

Statistical analysis

Continuous data was expressed as mean ± standard deviation or median (range), and analyzed with the Student t test or the Wilcoxon rank sum test, as appropriate. Categorical data was expressed as frequencies and percentages and analyzed with the Pearson chi-square test or Fisher exact test, as appropriate. Subsequently, each variable was introduced into a logistic regression model. Factors with P values < 0.05 in univariable analyses were entered into the multivariable logistic regression model, screened using the backward method, where the inclusion criterion was $P < 0.05$. Statistical analyses were performed using SPSS 19.0 (IBM, Armonk, NY, USA). Two-sided P values < 0.05 were considered statistically significant.

Results

Thirty-six patients (36/382, 9.4%) had PCH (Supplementary Table S1). Of these, 17 (17/36, 47.2%, or 17/382, 4.5%) had asymptomatic PCH. Multivariable analysis showed that serum total cholesterol (OR = 0.510, 95%CI 0.312–0.832, P = 0.007), cerebral microbleeds (OR = 6.251, 95%CI 2.220–17.601, P = 0.001), and antithrombotic drugs history (OR =

Table 1 Univariable logistic regression of factors associated with cerebral hemorrhage

	Odds ratio	95% confidence interval	P
TOAST classification			
LAA vs. SUE	1.011	0.248–4.117	0.988
SAA vs. SUE	0.383	0.121–1.214	0.103
CE vs. SUE	–	–	–
SOE vs. SUE	1.386	0.470–3.517	0.625
Hypertension history	1.843	0.664–5.119	0.241
Hypertension classification	1.233	0.887–1.713	0.212
SBP	1.000	0.983–1.018	0.969
DBP	0.998	0.966–1.032	0.927
Diabetes	1.415	0.675–2.967	0.358
Fasting blood glucose	1.039	0.901–1.196	0.600
HbA1c	1.164	0.969–1.400	0.105
LDL	0.511	0.313–0.836	0.008
HDL	0.623	0.155–2.507	0.505
TC	0.498	0.318–0.778	0.002
TG	1.006	0.616–1.642	0.980
Uric acid	1.003	0.999–1.007	0.100
Creatinine	1.011	0.997–1.025	0.133
Microbleeds	7.000	2.742–17.867	<0.001
Microbleeds score	1.062	1.006–1.121	0.030
Hemorrhagic transformation	0.265	0.034–2.078	0.206
Prominent vessel sign on SWI	3.086	0.841–11.328	0.089
History of antithrombotic drugs	3.143	1.176–8.400	0.022
Brain white matter degeneration score	1.357	1.090–1.690	0.006

TOAST Trial of Org10172 in Acute Stroke Treatment, *LAA* large-artery atherosclerosis, *SAA* small-artery occlusion, *CE* cardio-embolism, *SOE* stroke of other demonstrated etiology, *SUE* stroke of other undemonstrated etiology, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *TC* total cholesterol, *TG* triglycerides

3.213, 95%CI 1.018–10.145, $P = 0.047$) were independently associated with PCH (Tables 1 and 2). Asymptomatic PCH had similar demographic, neuroimaging, and biochemical characteristics with symptomatic PCH (Supplementary Table S2).

Discussion

The study aimed to analyze the prevalence of PCH in patients with acute ischemic stroke using SWI and to analyze the factors associated with PCH in those patients. Thirty-six (9.4%) patients were found to have PCH. Multivariable analysis

results showed that TC, existence of CMBs on SWI, and medication history of antithrombotic drugs were independently associated with the presence of a PCH in patients with ischemic stroke. There were no differences in clinical characteristics between previous symptomatic and asymptomatic PCH.

In the present study, the frequency of PCH was 9.4%, or 4.5% for asymptomatic PCH, which was slightly lower than in previous studies [14, 15]. The discrepancies could be due to the selection of the subjects and geographical regions, as well as to different imaging protocols.

Patients with ischemic stroke should promptly receive antithrombotic therapy for secondary prevention if they do not have any significant contraindication, but for those with both

Table 2 Multivariable regression analysis of factors associated with cerebral hemorrhage

	Odds ratio	95% confidence interval	P
Total cholesterol	0.510	0.312–0.832	0.007
Cerebral microbleeds	6.251	2.220–17.601	0.001
Use history of antithrombotic drugs	3.213	1.018–10.145	0.047

Factors with *P* values < 0.05 in univariable analyses were tested using a backward method

acute ischemic stroke and PCH, symptomatic or not, long-term aggressive antithrombotic therapy should be used with caution after considering the risks and benefits to avoid re-bleeding [3–7]. There were no long-term randomized studies addressing this issue. There is a marked paucity of evidence to guide clinicians when planning the long-term management of patients with cerebral hemorrhage and cogent indications for antithrombotic therapy. Recently, a randomized controlled trial, "The REstart or STop Antithrombotics Randomised Trial (RESTART) after stroke due to intracerebral haemorrhage," has been registered to compare starting versus avoiding anti-platelet drugs for adults surviving antithrombotic-associated ICH at 122 hospital sites in the UK [16].

CMB can be associated with poor prognosis of stroke [17, 18]. A recent study reported in White and Chinese patients with ≥ 5 CMBs withholding antiplatelet drugs during the first year after transient ischemic attack/ischemic stroke may be inappropriate; however, the risk of ICH may outweigh any benefit thereafter [19].

The present study found that there were more patients suffering from CMBs in patients with PCH compared with patients without PCH, and CMBs independently associated with existence of PCH. Thus, for patients with ischemic stroke, it could be necessary to perform SWI examination to promptly discover CMBs, as well as PCH, in order to guide antithrombotic medication.

The proper management of patients with acute ischemic stroke and PCH remains controversial [3–7, 20, 21]. Our study found the PCH was not uncommon in acute ischemic stroke patients and antithrombotic medication should be used with more caution after considering risk and benefit. The present study also suggests that there were no differences in clinical characteristics between symptomatic and asymptomatic PCH, making the latter easy to be missed, which could influence the outcomes of antithrombotic therapy and increase the risk of re-bleeding. The present study suggests that SWI could be a proper imaging modality for identifying patients with asymptomatic PCH, hence guiding the therapeutic strategy and patient management.

The limitations are presented as Supplemental Material.

Conclusion

In this study of patients admitted in national stroke centers for acute ischemic stroke and who underwent conventional MRI and SWI and cranial CT, 9.4% were found to have a PCH. Total cholesterol, the presence of CMBs on SWI, and history of antithrombotic drugs were independently associated with the presence of PCH in patients with acute ischemic stroke. Asymptomatic PCH, which is easier to be missed but has similar characteristics of demographic, neuroimaging, and serum biochemical testing with symptomatic PCH, should draw much attention. Hence, implementing routine cranial SWI examination could show PCH more sensitively, allowing the optimal management of these patents in order to prevent re-bleeding and worsening of the clinical outcomes.

References

1. Inohara T, Xian Y, Liang L, Matsouaka RA, Saver JL, Smith EE, Schwamm LH, Reeves MJ, Hernandez AF, Bhatt DL, Peterson ED, Fonarow GC (2018) Association of intracerebral hemorrhage among patients taking non-vitamin K antagonist vs vitamin K antagonist oral anticoagulants with in-hospital mortality. JAMA 319(5):463–473. https://doi.org/10.1001/jama.2017.21917
2. Tsivgoulis G, Lioutas VA, Varelas P, Katsanos AH, Goyal N, Mikulik R, Barlinn K, Krogias C, Sharma VK, Vadikolias K, Dardiotis E, Karapanayiotides T, Pappa A, Zompola C, Triantafyllou S, Kargiotis O, Ioakeimidis M, Giannopoulos S, Kerro A, Tsantes A, Mehta C, Jones M, Schroeder C, Norton C, Bonakis A, Chang J, Alexandrov AW, Mitsias P, Alexandrov AV (2017) Direct oral anticoagulant- vs vitamin K antagonist-related nontraumatic intracerebral hemorrhage. Neurology 89(11):1142–1151. https://doi.org/10.1212/WNL.0000000000004362
3. Gulati S, Solheim O, Carlsen SM, Øie LR, Jensberg H, Gulati AM, Madsbu MA, Giannadakis C, Jakola AS, Salvesen Ø (2018) Risk of intracranial hemorrhage (RICH) in users of oral antithrombotic drugs: Nationwide pharmacoepidemiological study. PLoS One 13(8):e0202575. https://doi.org/10.1371/journal.pone.0202575

4. Perry LA, Berge E, Bowditch J, Forfang E, Rønning OM, Hankey GJ, Villanueva E, Al-Shahi Salman R (2017) Antithrombotic treatment after stroke due to intracerebral haemorrhage. Cochrane Database Syst Rev 5:CD012144. https://doi.org/10.1002/14651858.CD012144.pub2

5. Roquer J, Vivanco Hidalgo RM, Ois A, Rodríguez Campello A, Cuadrado Godia E, Giralt Steinhauer E, Gómez González A, Soriano-Tarraga C, Jiménez Conde J (2017) Antithrombotic pretreatment increases very-early mortality in primary intracerebral hemorrhage. Neurology 88(9):885–891. https://doi.org/10.1212/WNL.0000000000003659

6. Pasquini M, Charidimou A, van Asch CJ, Baharoglu MI, Samarasekera N, Werring DJ, Klijn CJ, Roos YB, Al-Shahi Salman R, Cordonnier C (2014) Variation in restarting antithrombotic drugs at hospital discharge after intracerebral hemorrhage. Stroke 45(9):2643–2648. https://doi.org/10.1161/STROKEAHA.114.006202

7. Giakoumettis D, Alexiou GA, Vrachatis DA, Themistoklis K, Stathis P, Vavuranakis M, Themistocleous MS (2017) Antithrombotic treatment management in patients with intracerebral hemorrhage: reversal and restart. Curr Pharm Des 23(9):1392–1405. https://doi.org/10.2174/1381612822666161205111459

8. Thomas B, Somasundaram S, Thamburaj K, Kesavadas C, Gupta AK, Bodhey NK, Kapilamoorthy TR (2008) Clinical applications of susceptibility weighted MR imaging of the brain - a pictorial review. Neuroradiology 50(2):105–116

9. Tao XX, Li GF, Wu YL, Liu YS, Zhao Y, Shi YH, Zhuang MT, Hou TY, Zhao R, Liu FD, Wang XM, Shen Y, Cui GH, Su JJ, Chen W, Tang XM, Sun J, Liu JR (2017) Relationship between intracranial internal carotid artery calcification and enlarged cerebral perivascular space. Neuroradiology 59(6):577–586. https://doi.org/10.1007/s00234-017-1838-7

10. Gregoire SM, Chaudhary UJ, Brown MM, Yousry TA, Kallis C, Jager HR, Werring DJ (2009) The Microbleed Anatomical Rating Scale (MARS): reliability of a tool to map brain microbleeds. Neurology 73(21):1759–1766. https://doi.org/10.1212/WNL.0b013e3181c34a7d

11. Ayaz M, Boikov AS, Haacke EM, Kido DK, Kirsch WM (2010) Imaging cerebral microbleeds using susceptibility weighted imaging: one step toward detecting vascular dementia. J Magn Reson Imaging 31(1):142–148. https://doi.org/10.1002/jmri.22001

12. Haacke EM, Mittal S, Wu Z, Neelavalli J, Cheng YC (2009) Susceptibility-weighted imaging: technical aspects and clinical applications, part 1. AJNR Am J Neuroradiol 30(1):19–30. https://doi.org/10.3174/ajnr.A1400

13. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd (1993) Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 24(1):35–41

14. Aoki J, Shibazaki K, Saji N, Uemura J, Sakamoto Y, Kimura K (2014) Risk of intracerebral hemorrhage after thrombolysis in patients with asymptomatic hemorrhage on T2*. Cerebrovasc Dis 38(2):107–116. https://doi.org/10.1159/000365207

15. Lee SH, Kim BJ, Han MK, Park TH, Lee KB, Lee BC, Yu KH, Oh MS, Cha JK, Kim DH, Nah HW, Lee J, Lee SJ, Ko Y, Kim JG, Park JM, Kang K, Cho YJ, Hong KS, Choi JC, Kim JT, Choi K, Kim DE, Ryu WS, Kim WJ, Shin DI, Yeo M, Lee J, Lee JS, Gorelick PB, Bae HJ (2016) Should we exclude acute stroke patients with previous intracerebral hemorrhage from receiving intravenous thrombolysis? Int J Stroke 11(7):783–790. https://doi.org/10.1177/1747493016654289

16. Al-Shahi Salman R, Dennis MS, Murray GD, Innes K, Drever J, Dinsmore L, Williams C, White PM, Whiteley WN, Sandercock PAG, Sudlow CLM, Newby DE, Sprigg N, Werring DJ, RESTART collaborators (2018) The REstart or STop Antithrombotics Randomised Trial (RESTART) after stroke due to intracerebral haemorrhage: study protocol for a randomised controlled trial. Trials 19(1):162. https://doi.org/10.1186/s13063-018-2542-6

17. Wang DN, Hou XW, Yang BW, Lin Y, Shi JP, Wang N (2015) Quantity of cerebral microbleeds, antiplatelet therapy, and intracerebral hemorrhage outcomes: a systematic review and meta-analysis. J Stroke Cerebrovasc Dis 24(12):2728–2737. https://doi.org/10.1016/j.jstrokecerebrovasdis.2015.08.003

18. Chacon-Portillo MA, Llinas RH, Marsh EB (2018) Cerebral microbleeds shouldn't dictate treatment of acute stroke: a retrospective cohort study evaluating risk of intracerebral hemorrhage. BMC Neurol 18(1):33. https://doi.org/10.1186/s12883-018-1029-0

19. Lau KK, Lovelock CE, Li L, Simoni M, Gutnikov S, Küker W, Mak HKF, Rothwell PM (2018) Antiplatelet treatment after transient ischemic attack and ischemic stroke in patients with cerebral microbleeds in 2 large cohorts and an updated systematic review. Stroke 49(6):1434–1442. https://doi.org/10.1161/STROKEAHA.117.020104

20. Pennlert J, Asplund K, Carlberg B, Wiklund PG, Wisten A, Asberg S, Eriksson M (2015) Antithrombotic treatment following intracerebral hemorrhage in patients with and without atrial fibrillation. Stroke 46(8):2094–2099. https://doi.org/10.1161/STROKEAHA.115.009087

21. Use of Ottosen TP, Grijota M, Hansen ML, Brandes A, Damgaard D, Husted SE, Johnsen SP (2016) Antithrombotic therapy and long-term clinical outcome among patients surviving intracerebral hemorrhage. Stroke 47(7):1837–1843. https://doi.org/10.1161/STROKEAHA.116.012945