Acta Neurochir (2006) [Suppl] 96: 78–80

Printed in Austria

Spontaneous intracerebral hemorrhage in humans: hematoma enlargement, clot lysis, and brain edema

G. Wu[1], **G. Xi**[2], and **F. Huang**[1]

[1] Department of Neurosurgery, Huashan Hospital, Fudan University, Shanghai, China
[2] Department of Neurosurgery, University of Michigan Medical School, Ann Arbor, Michigan, USA

Summary

Early hematoma enlargement and delayed clot lysis contribute to brain injury after intracerebral hemorrhage (ICH). We investigated hematoma growth, clot lysis, and brain edema formation in patients with spontaneous ICH.

A total of 17 spontaneous ICH patients who received regular medication were chosen for this study. All patients had their first CT scan within 5 hours of onset of symptoms (day 0). The patients then underwent second, third, and fourth CT scans at 1, 3, and 10 days later. Hematoma size and absolute and relative brain edema volumes were measured. Hematoma enlargement was defined as a >33% increase in volume. Relative brain edema volume = absolute brain edema volume/hematoma size. Hematoma enlargement occurred in 4 of the 17 ICH patients (24%) within the first 24 hours. The hematoma sizes were reduced significantly at day 10 ($p < 0.05$) because of clot lysis. However, both absolute and relative brain edema increased gradually with time ($p < 0.01$).

These results suggest that delayed brain edema following ICH may result from hematoma lysis. This study also shows that early hematoma enlargement occurs in Chinese patients with ICH. Reducing early hematoma growth and limiting clot lysis-induced brain toxicity could be potential therapies for ICH.

Keywords: Intracerebral hemorrhage; brain edema; hematoma growth; hematoma lysis; computed tomography.

Introduction

Spontaneous intracerebral hemorrhage (ICH) is a common and often fatal stroke subtype lacking effective management [6]. ICH is estimated to account for 10–15% of all strokes in the United States [10]. The incidence of ICH is more common in China [17]. Brain edema contributes to brain damage after ICH [14]. Experimental and clinical investigations have demonstrated that early hematoma enlargement and delayed clot lysis contribute to ICH-induced brain injury [15]. The natural history and pathogenesis of hematoma and perihematomal edema in human ICH have not been well-studied. We investigated hematoma growth, clot lysis, and brain edema formation in Chinese ICH patients.

Materials and methods

Study design

In-patients who experienced spontaneous ICH ($n = 17$) in the Huashan Hospital at Fudan University between 2003 and 2004 were studied. All hematomas were located in the supratentorial area. Patients received regular medication. Exclusion parameters for this study included: 1) traumatic hemorrhage with initial or subsequent intraventricular extension, subsequent subarachnoid hemorrhage, or underlying aneurysm or vascular malformation, 2) death, or 3) undergoing surgical treatment within 10 days. All patients received non-contrast brain computed tomography (CT) scans within 6 hours of ICH onset. After the first CT scan, patients underwent second, third, and fourth CT scans at 1, 3, and 10 days after ICH onset. Hematoma enlargement was defined as a >33% increase in volume [2].

Measurement of hematoma and perihematomal edema volumes

All CT pictures were converted from CT machine to personal computer using the accessory software of the CT machine (e-Film), and NIH Image J 1.29 software (National Institutes of Health, USA) was used to analyze hematoma and edema volume.

We reset the calibration of the image according to the scale on the CT slices. Then the range of hematoma and perihematomal edema were marked out (for hematoma, the grey value was >130, and for the edema area, the grey value was 55–90). The area of hematoma and perihematomal edema of each CT slice was measured by NIH Image J. The above steps were repeated 3 times. Relative brain edema volume = absolute brain edema volume/hematoma size.

Statistical analysis

All data in this study are presented as mean ± SD. Data were analyzed with ANOVA using the Scheffe F test. Significance levels were measured at $p < 0.05$.

Results

A total of 17 patients were chosen for this study. Demographic and clinical features of the study patients are summarized in Table 1. All patients received noncontrast brain CT within 6 hours of ICH onset, and mean time was 2.6 hours after symptom onset. Ten patients had a history of hypertension (3–20 years) and 5 patients had a history of diabetes mellitus (4–13 years).

Hematoma enlargement occurred in 4 of the 17 ICH patients (24%) within the first 24 hours. Average hematoma sizes of all 17 patients were 20.9 ± 18.8, 23.8 ± 16.5, 21.2 ± 14.8, and 12.4 ± 10.3 cm^3 at days 0, 1, 3, and 10, respectively. The hematoma sizes were reduced significantly at day 10 ($p < 0.05$) because of clot lysis (Table 2, Fig. 1). However, both absolute and relative brain edema volumes increased gradually with time (absolute edema: 46.4 ± 30.1 at day 10 vs. 20.4 ± 13.2 cm^3 at day 0, $p < 0.05$; relative edema: 6.1 ± 6.5 at day 10 vs. 1.3 ± 0.8 at day 0, $p < 0.05$; Table 2). Figure 1 shows serial CT scans in 2 ICH patients.

Discussion

Our study demonstrates that early hematoma enlargement contributes to brain injury in Chinese ICH patients. Hematoma enlargement occurred in 4 of 17 ICH patients (24%) within the first 24 hours.

Several recent investigations evaluated the rate of hematoma enlargement after initial presentation [1, 2, 4, 7]. Early enlargement of the hematoma after the ictus is associated with midline shift and accelerates neurological deterioration [1, 16]. The precise mechanisms of hematoma growth are not known, but most hematoma enlargement occurs within the first 24 hours [2, 7]. Broderick *et al*. [1] recognized that early hematoma growth is associated with early neurological deterioration. An ongoing clinical trial focuses on early treatment with activated Factor VIIa aimed at preventing hematoma enlargement and reducing ICH-induced brain injury [8].

We also found that hematoma size decreases and perihematomal brain edema increases during the first 10 days after ICH in humans, suggesting delayed brain edema following ICH may result from hematoma lysis. Other studies have demonstrated that perihematomal edema peaks several days after ICH [3, 11]. In rats, brain edema peak occurs on the third or fourth day after experimental ICH [13]. This delayed brain edema may be related to erythrocyte lysis, because infusion of packed erythrocytes causes edema after about 3 days but not earlier when the erythrocytes remain intact [13]. A clinical study of brain edema after ICH also indicates that delayed edema is related to significant midline shift after ICH [16].

Delayed brain edema in ICH patients may be due to erythrocyte lysis and iron toxicity. Our previous studies demonstrated that an intracerebral infusion of hemoglobin and its degradation products, hemin, iron, and bilirubin, cause the formation of brain edema within 24 hours. Hemoglobin itself induces heme oxygenase-1 up-regulation in the brain, and heme oxygenase inhibition by tin-protoporphyrin reduces hemoglobin-induced brain edema. In addition, an intraperitoneal injection of a large dose of deferoxamine, an iron chelator, attenuates brain edema induced by hemoglobin. These results indicate that hemoglobin

Table 1. *Clinical data after admission.*

Gender (n)	Male (10), female (7)
Age, y	59 ± 13
Systolic pressure, mmHg	176 ± 26
Diastolic pressure, mmHg	105 ± 13
Blood glucose, mM	9 ± 3
Glasgow Coma Scale	11 ± 3
Hematoma location, n (%)	
– Right basal ganglia	6 (36)
– Left basal ganglia	4 (24)
– Right temporal lobe	2 (12)
– Left temporal lobe	3 (18)
– Right parieto-occipital	1 (6)
– Right frontal lobe	1 (6)

Table 2. *Volumes of hematoma and perihematomal brain edema.*

Volume	Day 0	Day 1	Day 3	Day 10
Volume of hematoma (cm^3)	20.9 ± 18.8	23.8 ± 16.5	21.2 ± 14.8	$12.4 \pm 10.2^{\#}$
Absolute edema volume (cm^3)	20.4 ± 13.2	$30.7 \pm 15.4^{\#}$	42.6 ± 23.8	46.4 ± 30.1
Relative edema volume	1.3 ± 0.8	1.7 ± 1.1	2.5 ± 1.7	6.1 ± 6.5

$^{\#}$ $p < 0.05$ vs. day 0.

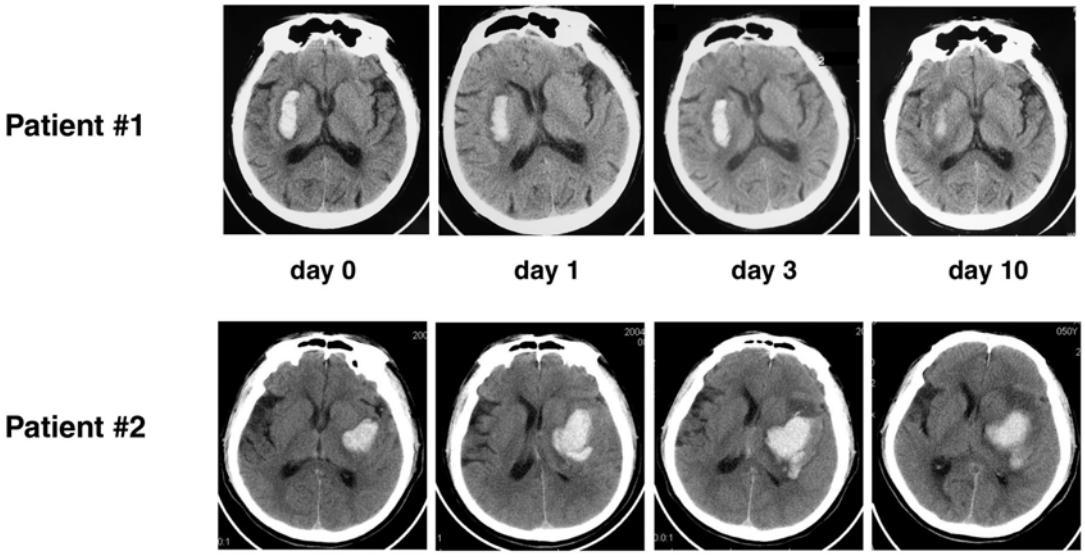

Fig. 1. Serial CT scans of 2 ICH patients

causes brain injury by itself and through its degradation products [5]. Also, investigations have demonstrated that iron overload occurs in the brain after ICH, and iron chelation with deferoxamine reduces perihematomal edema [9, 12].

In conclusion, early hematoma enlargement occurred in our study population of Chinese ICH patients, and delayed perihematomal edema development was associated with erythrocyte lysis. Reducing early hematoma growth and limiting clot lysis-induced brain toxicity could be potential therapies for ICH.

References

1. Broderick JP, Brott TG, Tomsick T, Barsan W, Spilker J (1990) Ultra-early evaluation of intracerebral hemorrhage. J Neurosurg 72: 195–199
2. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, Spilker J, Duldner J, Khoury J (1997) Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke 28: 1–5
3. Enzmann DR, Britt RH, Lyons BE, Buxton JL, Wilson DA (1981) Natural history of experimental intracerebral hemorrhage: sonography, computed tomography and neuropathology. AJNR Am J Neuroradiol 2: 517–526
4. Fujii Y, Tanaka R, Takeuchi S, Koike T, Minakawa T, Sasaki O (1994) Hematoma enlargement in spontaneous intracerebral hemorrhage. J Neurosurg 80: 51–57
5. Huang FP, Xi G, Keep RF, Hua Y, Nemoianu A, Hoff JT (2002) Brain edema after experimental intracerebral hemorrhage: role of hemoglobin degradation products. J Neurosurg 96: 287–293
6. Kase CS, Caplan LR (1994) Intracerebral Hemorrhage. Butterworth-Heinemann, Boston
7. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T (1996) Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. Stroke 27: 1783–1787
8. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T; Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators (2005) Recombinant activated factor VII for acute intracerebral hemorrhage. N Eng J Med 352: 777–785
9. Nakamura T, Keep R, Hua Y, Schallert T, Hoff JT, Xi G (2004) Deferoxamine-induced attenuation of brain edema and neurological deficits in a rat model of intracerebral hemorrhage. J Neurosurg 100: 672–678
10. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF (2001) Spontaneous intracerebral hemorrhage. N Engl J Med 344: 1450–1460
11. Tomita H, Ito U, Ohno K, Hirakawa K (1994) Chronological changes in brain edema induced by experimental intracerebral hematoma in cats. Acta Neurochir Suppl (Wien) 60: 558–560
12. Wu J, Hua Y, Keep RF, Nakamura T, Hoff JT, Xi G (2003) Iron and iron-handling proteins in the brain after intracerebral hemorrhage. Stroke 34: 2964–2969
13. Xi G, Keep RF, Hoff JT (1998) Erythrocytes and delayed brain edema formation following intracerebral hemorrhage in rats. J Neurosurg 89: 991–996
14. Xi G, Keep RF, Hoff JT (2002) Pathophysiology of brain edema formation. Neurosurg Clin N Am 13: 371–383
15. Xi G, Fewel ME, Hua Y, Thompson BG, Hoff J, Keep R (2004) Intracerebral hemorrhage: pathophysiology and therapy. Neurocrit Care 1: 5–18
16. Zazulia AR, Diringer MN, Derdeyn CP, Powers WJ (1999) Progression of mass effect after intracerebral hemorrhage. Stroke 30: 1167–1173
17. Zhang LF, Yang L, Hong Z, Yuan GG, Zhou BF, Zhao LC, Huang YN, Chen J, Wu YF; Collaborative Group of China Multicenter Study of Cardiovascular Epidemiology (2003) Proportion of different subtypes of stroke in China. Stroke 34: 2091–2096

Correspondence: Fengping Huang, Department of Neurosurgery, Huashan Hospital, Fudan University, 12 Wulumuqi Zhong Road, Shanghai 200040 China. e-mail: fengpinghuang@hotmail.com