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No Awakening in Supratentorial Intracerebral Hemorrhage Is Potentially Caused by Sepsis-Associated Encephalopathy

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Manuscript Preparation E
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Background: Acute supratentorial intracerebral hemorrhage (sICH) with secondary sepsis is increasing in frequency. We investigated whether no awakening (NA) after sICH with coma is potentially caused by sepsis-associated encephalopathy (SAE).





Material/Methods: A case-control study of 147 recruited sICH cases with NA and 198 sICH controls with subsequent awakening (SA) was performed at 2 centers in China. All patients underwent brain computed tomography (CT) scans on admission. The odds ratio (OR) of NA was calculated using logistic regression.

Results: During the study period, 56.5% (83/147) of the patients with sICH with coma and NA had SAE, and 10% (20/198) with sICH with coma and SA had SAE; this difference between the 2 groups was significant ($p < 0.000$). The sICH patients with coma and NA exhibited a longer median time from onset to coma (2.0 days vs. 0.5 days), more frequent confirmed infection (98.0% vs. 24.2%), and a higher Sequential Organ Failure Assessment (SOFA) score (6.3 ± 1.5 vs. 3.4 ± 0.8). These patients also exhibited lower hematoma volume (28.0 ± 18.8 vs. 38.3 ± 24), a lower initial National Institutes of Health Stroke Scale score (19.5 ± 6.6 vs. 30.3 ± 6.8), more frequent brain mid-line shift (59.2% vs. 27.8%), more frequent diffuse cerebral swelling (64.6% vs. 16.0%), and higher 30-day mortality (54.4% vs. 0.0%) than the patients who did awaken. Logistic multivariable regression analyses revealed that only a higher SOFA score (OR, 1.4; 95% CI, 1.079–1.767; $p = 0.010$) and SAE (OR, 4.0; 95% CI, 1.359–6.775; $p = 0.001$) were associated with NA events in patients with sICH.

Conclusions: NA in sICH patients with coma is potentially caused by secondary SAE.

MeSH Keywords: **Asepsis • Cerebral Hemorrhage • Outcome Assessment (Health Care)**

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Background

Sepsis is defined as a host reaction to infection that is characterized by life-threatening organ dysfunction [1] and has an annual incidence of 50.9 million from high-income country data worldwide [2]. Sepsis is associated with an increased risk of encephalopathy following systemic infection [3,4], which is known as sepsis-associated encephalopathy (SAE) or septic encephalopathy. SAE is the most common type of acute encephalopathy observed in various intensive care units (ICUs), with an incidence of 70% of septic patients [3,4]. The high risk of encephalopathy in septic patients may be attributed to systemic metabolic derangements, altered brain metabolism, abnormal neurotransmitters, inflammatory cytokines, blood-brain barrier dysfunction, bacteria and/or endotoxins that directly affect the central nervous system [5,6], coupled with an altered response to systemic inflammation due to infection. Therefore, SAE is a significant risk factor for increased morbidity and mortality after infection [7].

Acute supratentorial intracerebral hemorrhage (sICH) exhibits a 28-day mortality rate of 43.0% [8]. The incidence of intracerebral hemorrhage (ICH) patients who are at high risk for infections has increased [9–11], and as a result, the number of patients with ICH and SAE is also increasing. The mortality rate of SAE ranges from 51.0 to 71.9% [7], but the prognosis for sICH concurrent with SAE may be worse. However, few reports have discussed the prognostic factors that affect the neurological outcome of sICH in patients with SAE. We thus examined the frequency of SAE after sICH in patients with coma and assessed whether the early burden of no awakening (NA) was associated with an increased risk of SAE.

Material and Methods

Study setting

This study was a retrospective case-control study of all registered patients within 2 different time periods at 2 adult neurologic ICUs in China (Jun 1, 2010, through Jul 31, 2012, at Affiliated Shuyang People's Hospital, Xuzhou Medical University, and Jan 1, 2008, through Dec 31, 2009, at Affiliated Pingxiang Hospital, Southern Medical University). NA was defined as persistent severely disturbed consciousness, with a Glasgow Coma Scale (GCS) score <9 in the absence of sedation and a lack of awakening with loud calls before hospital discharge or death. In total, 147 sICH patients with NA were age- and sex-matched with 198 sICH patients with subsequent awakening (SA). The Ethics Committee on Clinical Research of Shuyang People's Hospital, China, approved the study. The study was in full compliance with the Helsinki Declaration, and written informed consent was obtained from the nearest relative or a

person who had been designated to give consent on admission of the patient.

Patient identification

Based on the International Statistical Classification of Diseases 10th Revision (ICD-10) by the WHO, released in 1994, data were searched retrospectively to identify all patients with a primary diagnosis of sICH with a coma event (code I61.9, R40.2) in a 4-year period.

The diagnostic criteria for SAE in sICH patients with coma, used to determine eligibility for study inclusion, are as follows: (1) organ dysfunction caused by infection [1], and (2) coma that could not be explained by isolated sICH, e.g., if the hematoma was reduced or absorbed, the patient still did not wake up from the coma. The following exclusion criteria were used for SAE: 1) presenting evidence of meningitis/encephalitis; 2) presenting evidence of significant ICH growth; 3) presenting other acute primary encephalopathy, including an endocrine disorder, isolated hyponatremia or hyponatremia; and 4) presenting evidence of organ dysfunction due to the effects of sedatives or other medicine.

Clinical assessment

All patients underwent an initial brain CT scan on admission and at least 1 repeat brain CT after coma onset. The most recent CT after coma onset was used for all patients. Hematoma volumes on admission and the closest time of rebleeding were determined using the standard ABC/2 formula (where A is the longest diameter of the hematoma, B is the widest diameter of the hematoma, and C is the layer thickness of the hematoma) [12]. A midline shift on head CT was measured as described previously [13]. Cisterns were assessed using Marshall Scale criteria [14].

The infection was identified based on the approach established by the Centers for Disease Control and Prevention [15]. Confirmed infection was defined as positive microorganisms found in body fluid culture or a focus of infection found by imaging, such as lung CT or chest radiography. Suspected infection was defined primarily as fulfilling ≥ 2 systemic inflammatory response syndrome (SIRS) criteria, with exclusion of non-infectious fever, central high fever, and thyroid crisis. Based on the results, patients with infection were classified into the NA group or SA group. The clinical data on infections in the NA group were from before coma.

Organ failure was defined as a Sequential Organ Failure Assessment (SOFA) score ≥ 2 for a particular organ after the onset of infection [16]. The following were considered to be equivalent to a SOFA score ≥ 2 for a particular organ (on a scale from

0 to 4, with higher scores indicating more severe organ failure): GCS score <13=brain failure; bilateral infiltrates on chest thorax radiography and an arterial oxygen pressure/fraction of inspired oxygen ratio ($\text{PaO}_2/\text{FiO}_2$) ≤ 300 or a need for supplemental oxygen to maintain >90% oxygen saturation=respiratory failure; hypotension (systolic blood pressure (SBP) <90 mmHg, mean arterial pressure <65 mmHg or decrease of >40 mmHg in the systolic pressure)=circulation failure; total serum bilirubin >33 $\mu\text{mol/L}$ =liver failure; creatinine >171 $\mu\text{mL/L}$ =renal failure; and platelet count $\leq 100 \times 10^9/\text{L}$ =blood failure.

The following data were analyzed in sICH patients with NA or SA events: age, sex, underlying disease, hematoma location, hemorrhage growth, hematoma volume, accompanying intraventricular hemorrhage, initial National Institutes of Health stroke scale (NIHSS) score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, body temperature, blood pressure, heart rate, respiratory rate, creatinine, bilirubin, serum glucose, white blood cell (WBC) count, platelet count, SOFA score, chest X-ray or CT scan, and body fluid cultures. We also recorded the GCS score, the onset-to-coma time, and the length of ICU stay. Outcomes were assessed at 30-day follow-up.

Related definition

Significant ICH growth was defined as hematoma enlargement >33% [17] or hematoma enlargement that led to a brain herniation. Brain herniation was divided into uncal and central types [18]. A downward displacement of the brain through the tentorial opening was noted in both types of herniation. Central herniation was defined as compression of the Ascending Reticular Activating System (ARAS) in the central diencephalon, radiological midline shift and peri-mesencephalic cistern compression, with clinical stupor or coma. Uncal herniation patients were more likely to exhibit unilateral uncal gyrus downward displacement, midbrain compression and ARAS compression than bilateral displacement; radiological midline shift with third nerve compression and clinical coma, pupil asymmetry >2 mm, and loss of reactivity to light.

Statistical methods

The quantitative results in each group are expressed as the mean \pm standard deviation (SD) or the median (interquartile range (IQR)), and n (%) is used to express qualitative values. Patients without awakening were compared with patients with awakening using univariate analysis. Fisher's exact test and the Mann-Whitney *U* test were used to examine the relationship between baseline patient variables. Continuous variables were compared using Student's *t* test. Multivariate regression analysis was performed with age and sex adjustment. All *p*-values were 2-sided, and significance was set at *p*<0.05.

Statistical calculations were performed using a proprietary computerized statistics package (SPSS 10.0).

Results

There were no statistically significant differences in age, sex, hemorrhage location, or underlying diseases. The onset-to-coma time (median) was 2.0 days in the NA group and 0.5 days in the SA group. The difference in the onset-to-coma time between the 2 groups was statistically significant (*p*=0.001). The GCS score and the length of ICU stay were also significantly different (*p*<0.05) between the 2 groups. Hematoma aspiration was slightly less frequent in patients with NA than in patients with SA, but the difference was not significant (*p*>0.05). During the follow-up for patients with or without awakening, the mortality rate at 30 days was 54.4% (80/147) in the sICH patients with NA and 0.0% (0/198) in the sICH patients with SA events (Table 1).

Table 2 shows the clinical manifestations of infections in sICH patients with NA and SA. In total, 83 (56.5%) patients who met the sepsis criteria were diagnosed in the NA group, whereas only 20 (10%) patients with sepsis were diagnosed in the SA group. A difference in the prevalence of sepsis between the 2 groups was noted (*p*=0.000). The median time from onset to infection in these septic patients was 36 hours (range 1–168 hours). The rates of fulfilling ≥ 2 SIRS criteria (67.3% vs. 22.2%, *p*=0.000), confirmed infection (98.0% vs. 24.2%, *p*=0.000), and hospital-acquired infection (38.9% vs. 16.7%, *p*=0.000) were higher in the NA group than in the SA group. The most common infection focus in patients with NA was primarily respiratory or blood infection.

Table 3 shows the results of the univariate analysis. We found no difference in respiratory rate, elevated WBC count, platelet count, acute respiratory failure, acute renal failure, hyperglycemia, acute hepatic failure, acute seizures, APACHE II score, basal cistern compression, central herniation, uncal herniation, or hemorrhagic transformation between patients with NA and SA (*p*>0.05). However, temperature (38.0 ± 1.3 vs. 37.0 ± 1.0 , *p*=0.000), pulse rate (94.8 ± 16.2 vs. 84.3 ± 15.1 , *p*=0.003), SBP (162.1 ± 40.5 vs. 188.0 ± 34.7 , *p*=0.002), diastolic blood pressure (DBP) (95.1 ± 26.2 vs. 107.9 ± 16.7 , *p*=0.007), SAE (56.5% vs. 10%, *p*=0.000), septic shock (8.2% vs. 0.0%, *p*=0.000), SOFA score (6.3 ± 1.5 vs. 3.4 ± 0.8 , *p*=0.000), midline shift (59.2% vs. 27.8%, *p*=0.000), diffuse cerebral swelling (64.9% vs. 16.0%, *p*=0.000), hematoma volume (28.0 ± 18.8 vs. 38.3 ± 24.4 , *p*=0.035), and initial NIHSS score (19.5 ± 6.6 vs. 30.3 ± 6.8 , *p*=0.000) exhibited significant differences between the groups. However, in the multivariable regression analysis, only a higher SOFA score (OR, 1.4; 95% CI, 1.079–1.767; *p*=0.010) and SAE (OR, 4.0; 95% CI, 1.359–6.775; *p*=0.001) were associated with NA events in patients with sICH (Table 4).

Table 1. Baseline characteristics in supratentorial intracerebral hemorrhage patients with NA or SA.

Episodes	NA (N=147)	SA (N=198)	P value
Male gender (%)	99 (67.3)	115 (58.0)	0.093
Age (years, mean ±SD)	60.8±11.4	61.4±10.7	0.812
Location of hemorrhage			
Striato-capsula (%)	83 (56.5)	123 (62.0)	0.318
Lobar (%)	52 (35.4)	55 (28.0)	0.158
Thalamus (%)	12 (8.2)	20 (10.0)	0.579
Intraventricular extension (%)	32 (21.8)	59 (29.8)	0.109
Underlying diseases			
Hypertension (%)	119 (81.0)	190 (96.0)	0.000
Diabetes (%)	12 (8.2)	28 (14.0)	0.092
Previous stroke (%)	24 (16.3)	40 (20.0)	0.402
Hospitalized conditions and outcome			
Median OCT (days, range)	2.0 (13.9)	0.5 (1.0)	0.001
Initial GCS score (mean ±SD)	10.2±1.5	8.6±1.6	0.008
Hematoma aspiration (%)	21 (14.3)	44 (22.2)	0.071
Mechanical ventilation (%)	76 (51.7)	103 (52.0)	1.000
SOFA score (mean ±SD)	6.3±1.5	3.4±0.8	0.000
Length of ICU (days)	10.5±9.4	7.0±3.9	0.001
Vegetative state (%)	47 (32.0)	0 (0.0)	0.000
Coma (%)	20 (13.6)	0 (0.0)	0.000
Mortality in 30 days (%)	80 (54.4)	0 (0.0)	0.000

NA – no awakening; SA – subsequent awakening; OCT – onset-to-coma time; GCS – Glasgow Coma Scale; SOFA – sequential organ failure assessment.

Table 2. Manifestation of infections between ICH patients with NA and SA.

Manifestation of infection	Data before coma in NA (N=147)	Data at admission in SA (N=198)	P value
Sepsis (%)	83 (56.5)	20 (10.0)	0.000
SIRS ≥2 criteria (%)	99 (67.3)	44 (22.2)	0.000
Confirmed infection (%)	144 (98.0)	48 (24.2)	0.000
Pneumonia	64 (44.4)	20 (41.7)	0.867
Tracheobronchial	16 (11.1)	18 (37.5)	0.000
Intestinal tract	4 (2.8)	1 (2.1)	1.000
Central nervous system	4 (2.8)	1 (2.1)	1.000
Urinary tract	8 (5.6)	4 (8.3)	0.499
Gram-Positive for blood	32 (22.2)	4 (8.3)	0.034
Gram-Negative for blood	16 (11.1)	0 (0.0)	0.000
Hospital-acquired infection (%)	56 (38.9)	8 (16.7)	0.000

NA – no awakening; SA – subsequent awakening; SIRS – systemic inflammatory response syndrome.

Table 3. Univariate analyses of supratentorial intracerebral hemorrhage patients with NA or SA.

Episodes	NA (N=147)	SA (N=198)	P value
Body temperature (°C)	38.0±1.3	37.0±1.0	0.000
Heart rate (beats/min)	94.8±16.2	84.3±15.1	0.003
Respiratory rate (breaths/min)	24.4±6.0	23.4±6.0	0.442
leukocyte count (×10 ⁹ /l)	14.8±5.7	12.3±6.4	0.066
Platelet count (×10 ⁹ /l)	220.3±40.3	219.9±30.6	0.966
SBP, mmHg, mean±SD	162.1±40.5	188.0±34.7	0.002
DBP, mmHg, mean±SD	95.1±26.2	107.9±16.7	0.007
SAE (%)	83 (56.5)	20 (10.0)	0.000
Acute respiratory failure (%)	36 (24.5)	32 (16.2)	0.057
Pneumonia (%)	56 (38.1)	57 (28.8)	0.082
Septic shock (%)	12 (8.2)	0 (0)	0.000
Acute renal failure (%)	20 (13.6)	20 (10.0)	0.357
Acute hepatic failure (%)	8 (5.4)	5 (2.5)	0.252
Acute seizures (%)	16 (10.9)	15 (7.6)	0.342
Hyperglycemia (%)	5 (13.5)	4 (8.0)	0.404
APACHE II score, mean ±SD	24.6±6.4	25.8±6.3	0.084
SOFA, mean±SD	6.3±1.5	3.4±0.8	0.000
Initial NIHSS score, mean ±SD	19.4±6.6	30.2±6.8	0.000
CT characteristics			
Midline shift (%)	87 (59.2)	55 (27.8)	0.000
Basal cisterns compressed (%)	123 (83.7)	176 (88.9)	0.200
Diffuse cerebral swelling (%)	95 (64.6)	32 (16.0)	0.000
Central herniation (%)	95 (64.6)	138 (69.7)	0.353
Uncal herniation (%)	36 (24.5)	34 (17.2)	0.105
Hematoma growth (%)	12 (8.2)	24 (12.1)	0.286
Hematoma volume (mL, mean ±SD)	28.0±18.8	38.3±24.4	0.035

NA – no awakening; SA – subsequent awakening; SBP – systolic blood pressure; DBP – diastolic blood pressure; SAE – sepsis-associated encephalopathy; APACHE II – acute physiology and chronic health evaluation II; SOFA – sequential organ failure assessment.

Table 4. The multivariable analysis of supratentorial intracerebral hemorrhage patients with NA or SA.

Variable	NA (N=147)	SA (N=198)	OR (95%CI)	P volume
SOFA score	6.3±1.5	3.4±0.8	1.4 (1.079–1.767)	0.010
SAE (%)	83 (56.5)	20 (10.0)	4.0 (1.359–6.775)	0.001

NA – no awakening; SA – subsequent awakening; SOFA – sequential organ failure assessment.

Discussion

A high prevalence of infection in patients with ICH has been demonstrated in certain studies [9–11]. Sepsis is not rare in patients with stroke [10,19,20]. SAE is secondary to sepsis, but positive blood-based microbiological testing is only observed in one-third of cases [1]. However, sepsis has been newly defined as life-threatening organ dysfunction due to a dysregulated host response to infection [1], rather than a positive culture. Our study showed that the rate of confirmed infection and the SOFA score were significantly higher in patients with NA than in patients with SA, which supports the idea that sepsis most frequently occurs in patients with sICH with NA.

There are some well-known causes for the sICH that most commonly precipitate sICH, including a rupture of small penetrating arteries due to long-standing hypertension and other vascular abnormalities [21]. Probably, cerebral amyloid angiopathy is also relatively common [22], whereas coagulation dysfunctions are less common [23]. However, previous studies reported that 3 prognostic factors, namely, GCS score, ICH volume, and the presence of intraventricular hemorrhage, are related to neurological outcome in ICH patients [24–27], rather than its onset causes. Recent studies also emphasized that the initial neurological status, indicated by the hematoma volume, including early hematoma growth, was a contributing factor to poor outcomes in sICH [28,29]. Brain herniation appears to generally result from a supratentorial mass effect [30], which is associated with NA due to compression of the ARAS in the upper brainstem. However, the present study suggests that brain herniation events did not differ in frequency between the groups and that the hematoma volume in patients with NA was smaller than that in patients with SA; this difference was statistically significant. In fact, NA has a worse outcome. Therefore, the prognostic impact of hematoma volume on ICH patients may not be isolated.

In addition to hematoma volume, the univariate analysis showed that higher temperature, increased pulse rate, SAE, low SBP or DBP, septic shock, a higher SOFA score, a lower NIHSS score, midline shift, and diffuse cerebral swelling were significantly associated with NA. However, in the multivariable regression analysis, only a higher SOFA score and SAE were identified as independent predictors of NA in patients with sICH.

The present data demonstrate that patients with NA and SAE are significantly more frequent than patients with SA. Moreover, clinical NA was associated with a higher SOFA score. This evidence strongly supports the idea that NA in sICH patients is potentially caused by SAE.

However, what explains the NA events in sICH patients with secondary SAE? Our findings suggest 3 possible answers. First, the NA events were not explained by isolated sICH, as above; rather, secondary SAE can also lead to NA, and SAE patients had a low GCS score, which is consistent with a previous study [6]. Second, the higher SOFA score implied secondary brain failure. Previous studies suggested that the high mortality rate in SAE was mostly due to multiple organ failure (i.e., a higher SOFA score), such as brain, pulmonary, cardiovascular, renal, or hepatic dysfunction [6,31]. Third, our current study showed that the median time from symptom onset to brain failure (coma) was longer in the NA group than in the SA group, suggesting that patients with NA and sICH were more likely to have late-onset SAE. These 3 factors may jointly affect the host response and increase the risk of persistent NA, which contributes to apoptosis and necrosis. A recent study has found that acupuncture may protect the brain by changing expression of apoptotic factors in the brain [32]; therefore, it is worth recommending for ICH patients with NA.

Certain limitations in the present study should be considered. First, inflammatory cells and mediators are important confounding factors in ischemic brain injury [33], and subcortical white-matter ischemic lesions and microinfarctions are confirmed [5]. Therefore, brain MRI is more important than CT in ICH patients with SAE. However, MRI was not performed in this study. Second, although SAE was considered the cause of NA in patients, nonconvulsive status epilepticus (NCSE) has been recognized as another cause of impaired consciousness [34]. However, our patients with NA did not undergo electroencephalogram monitoring, so they may have been misdiagnosed and mistreated NCSE patients. Although our data included only patients with severe SAE and certain suddenly comatose patients whose coma could have been caused by NCSE, we excluded cases with non-infectious causes, cases of hematoma expansion, and cases with non-septic encephalopathy. Therefore, the high prevalence of SAE events in sICH patients with coma should not have been overestimated.

Conclusions

NA in sICH patients is potentially caused by secondary SAE. This result confirms research-based evidence that SAE in patients with sICH and coma need to be examined in further brain MRI studies.

Conflict of interests

None.

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