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Predictors of Late Neurological Deterioration After Spontaneous Intracerebral Hemorrhage

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Abstract

Background—Although intracerebral hemorrhage (ICH) is a common form of cerebrovascular disease, little is known about factors leading to neurological deterioration occurring beyond 48 h after hematoma formation. The purpose of this study was to characterize the incidence,

consequences, and associative factors of late neurological deterioration (LND) in patients with spontaneous ICH.

Methods—Using the Duke University Hospital Neuroscience Intensive Care Unit database from July 2007 to June 2012, a cohort of 149 consecutive patients with spontaneous supratentorial ICH met criteria for analysis. LND was defined as a decrease of two or more points in Glasgow Coma Scale score or death during the period from 48 h to 1 week after ICH symptom onset. Unfavorable outcome was defined as a modified Rankin Scale score of >2 at discharge.

Results—Forty-three subjects (28.9 %) developed LND. Logistic regression models revealed hematoma volume (OR = 1.017, 95 % CI 1.003–1.032, $p = 0.019$), intraventricular hemorrhage (OR = 2.519, 95 % CI 1.142–5.554, $p = 0.022$) and serum glucose on admission (OR = 2.614, 95 % CI 1.146–5.965, $p = 0.022$) as independent predictors of LND. After adjusting for ICH score, LND was independently associated with unfavorable outcome (OR = 4.000, 95 % CI 1.280–12.500, $p = 0.017$). In 65 subjects with follow-up computed tomography images, an increase in midline shift, as a surrogate for cerebral edema, was independently associated with LND (OR = 3.822, 95 % CI 1.157–12.622, $p = 0.028$).

Conclusions—LND is a common phenomenon in patients with ICH; further, LND appears to affect outcome. Independent predictors of LND include hematoma volume, intraventricular hemorrhage, and blood glucose on admission. Progression of perihematoma edema may be one mechanism for LND.

Keywords

Intracerebral hemorrhage; Neurological deterioration; Predictors; Outcome; Brain edema

Introduction

Primary intracerebral hemorrhage (ICH) is a major public health problem with an annual incidence of 10–30 per 100,000 population, accounting for 2 million (10–15 %) of about 15 million strokes worldwide each year [1]. Several studies have investigated early neurological deterioration in patients with ICH [2–4]. This form of secondary injury develops within the first 24 or 48 h after symptom onset, and appears to carry a poor prognosis. Factors associated with early neurological deterioration include hematoma expansion, intraventricular hematoma (IVH) extension, fever, elevated white blood cell count, and higher blood pressure [2–5].

However, little is known about neurological deterioration occurring later than 48 h after ICH symptom onset, termed late neurological deterioration (LND). Given, the absence of effective treatment for ICH [1, 6], understanding LND may provide information regarding the evolution of disease pathophysiology and facilitate the design of therapeutic strategies to improve neurological function and outcome.

The current study sought to characterize the incidence and consequences of LND after ICH and identify factors that predicted LND in patients with spontaneous supratentorial ICH.

Methods

Patient Selection

After approval by the Duke University Institutional Review Board, data were abstracted from the Duke University Hospital Neuroscience Intensive Care Unit database of consecutive patients admitted after primary ICH from July 2007 to June 2012.

Patients were included in the study population if they had an admission diagnosis of supratentorial ICH confirmed by brain computed tomography (CT) imaging and the interval from the onset of symptom to admission was less than 24 h.

Exclusion criteria were: (1) ICH secondary to trauma, hemorrhagic conversion of ischemic stroke, cerebrovascular abnormality, intracranial tumor, intracranial venous sinus thrombosis, or coagulation abnormalities (including warfarin or other anticoagulants user); (2) aneurismal subarachnoid hemorrhage; (3) institution of comfort measures, death, or craniotomy prior to 48 h after symptom onset; (4) missing Glasgow Coma Scale (GCS) score data.

Data Collection

Demographics, past medical history, blood pressure, body temperature, serial neurological function examinations, laboratory results, and modified Rankin Scale (mRS) scores at discharge were extracted from the database.

Neurological function was assessed by daily GCS score. LND was defined as death or a decrease of two or more points in GCS score during the period from 48 h to 1 week after the ICH symptom onset compared to the GCS score at 48 h after ICH symptom onset. For those patients whose in-hospital length of stay (LOS) was less than 1 week, GCS scores were assumed to remain unchanged after discharge.

The time of symptom onset was defined as the witnessed moment of symptom onset or last known well time. The ICH score was calculated according to previous literature [7].

Unfavorable outcome was dichotomized into subjects with a mRS score at discharge ranging from 3 to 6 compared to patients with a mRS score of 0–2.

Imaging Analysis

Imaging results were extracted from the existing database. Diagnostic cranial CT images occurring on admission and follow-up CT images occurring during the first week after ICH onset were used for analyses. Follow-up CT images were defined, for patients with LND, as the first CT images performed within 48 h after the onset of LND and, for patients without LND, as the last CT images obtained during the period between 48 h and 1 week after ICH onset.

Anonymized CT data sets in DICOM format were loaded into the image analysis software (OsiriX version 4.0; Pixmeo, Geneva, Switzerland). Manual segmentation of the hematoma volumes were performed by an image analyst (CEH), and submitted to a board-certified neuroradiologist (PGK) for editing and review. IVH, defined as hyperdense material within

the ventricles not attributable to choroid plexus or calcification, was not included in the segmented hematoma volume [2]. Hematomas were classified as “deep” if they were located in the basal ganglia, thalamus, or internal capsule; all other hemorrhages were classified as “lobar” [2]. Midline shift (MLS) was determined by creating a line connecting the anterior and posterior insertions of the falx cerebri, and measuring a perpendicular distance from the line to the septum pellucidum, at the level of the foramen of Monro [5]. Hematoma expansion was defined as an increase in hematoma volume >20 % and MLS increase was defined as an increase in MLS >1 mm between baseline and follow-up CT images [5].

Statistical Analysis

Baseline characteristics were compared between patients with and without LND, which were performed by Chi square test or Fisher’s exact test for categorical variables and Wilcoxon rank-sum test for continuous variables. Multivariate analysis was performed using a logistic regression model to screen the independent predictors of LND. Initial predictor list included factors with a p value less than 0.1 in univariate analysis plus age and gender. Serum glucose concentration (GLU) was dichotomized, according to epidemiologic criteria (≤ 140 or >140 mg/dl). Backward and forward selection procedures were applied, respectively. And the criterion for entering variables was a p value <0.05 . The internal validity of the regression model was assessed by a tenfold cross validation analysis.

Logistic regression analysis was also performed to evaluate the relationship between LND and patients’ clinical outcome after adjusting for the dichotomized ICH score (≤ 2 or ≥ 3).

Subgroup analysis was performed in patients with follow-up CT scans available to test the association between hematoma expansion, MLS increase and LND. For variables found significant in univariate analysis, adjusted odds ratios were reported after controlling for the independent predictors of LND.

The robustness of our findings was assessed in several ways. First, sensitivity analysis was performed using a more conservative definition of LND, which required a decrease of two or more points in GCS score lasting for at least two measures or death during the period from 48 h to 1 week after symptom onset. Second, the study population was restricted to patients whose GCS score at 48 h after symptom onset was ≥ 5 . Third, the study population was restricted to patients whose in-hospital LOS was equal to or more than 1 week. Fourth, a definition of LND was based on NIH Stroke Scale (NIHSS) score, which required an increase ≥ 4 points in NIHSS score or death [8], in those patients with NIHSS score records available.

All statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). All p values were two-sided, with $p < 0.05$ considered statistically significant.

Results

Of the 216 patients with an admission diagnosis of supratentorial ICH admitted within the first 24 h after symptom onset, 149 patients were included in analyses (Fig. 1).

Demographics and clinical characteristics are summarized and compared between patients with and without LND in Table 1.

Incidence of LND

Of the 149 patients in the total study population, 43 patients (28.9 %) developed LND. Of the total study population, 12 patients (8.1 %) died within the period from 48 h to 1 week after the onset of symptom.

Predictors of LND

Univariate analyses of baseline predictors of LND are shown in Table 1. Patients with LND had higher GLU, total white blood cell count, and lower GCS score on admission compared to those without LND. There was no significant difference in age, gender, race/ethnicity, past medical history, blood pressure, body temperature, and platelet count on admission between the two groups.

The two groups had similar time intervals between symptom onset and initial CT imaging. Patients with LND had greater hematoma volume, MLS, and frequency of IVH on the baseline CT imaging compared to patients without LND.

The result of the multivariate logistic regression model is shown in Table 2. Backward and forward variable selections produced consistent results. Hematoma volume, IVH, and GLU were independent predictors of LND. A tenfold cross validation analysis showed 73 % accuracy for the logistic regression model to predict LND.

Relationship of LND and Clinical Outcome

Of the total study population, 2 (1.3 %) patients achieved a mRS score of 0 at discharge. A mRS score of 1 at discharge was found in 11 (7.4 %) patients, mRS of 2 in 27 (18.1 %) patients, mRS of 3 in 32 (21.5 %) patients, mRS of 4 in 35 (23.5 %) patients, mRS of 5 in 18 (12.1 %) patients, and mRS of 6 in 24 (16.1 %) patients.

Unfavorable outcome was more frequent in patients with LND than in those without LND (90.7 vs. 66.0 %, $p = 0.002$). After adjusting for the ICH Score, LND was associated with a fourfold increase in the odds of unfavorable outcome (OR = 4.000, 95 % CI 1.280–12.500, $p = 0.017$).

Associations Between LND and Hematoma Expansion and MLS Increase

Follow-up CT images fitting analysis criteria were obtained in 25 patients with and 40 patients without LND (Table 3). Patients with LND had a higher frequency of MLS increase compared to patients without LND (48.0 vs. 20.0 %, $p = 0.017$). The proportion of hematoma expansion did not differ significantly between the two groups. A logistic regression model indicated MLS increase was associated with LND independently (OR = 3.822, 95 % CI 1.157–12.622, $p = 0.028$) in this subgroup of 65 patients after adjusting for hematoma volume on admission, IVH, and GLU.

Sensitivity Analysis

A sensitivity analysis was performed using a stricter definition of LND, which required a decrease of two or more points in GCS score lasting for at least two measures or death. This analysis showed an incidence of 24.9 % for LND. Considering the potential limitation in detecting neurological deterioration in severe comatose patients, another sensitivity analysis reported LND occurred in 26.8 % of patients after excluding 11 patients with GCS score less than five at 48 h after symptom onset. The third sensitivity analysis reported an incidence of 32.0 % for LND in patients with an in-hospital LOS of 1 week or more. Since NIHSS has been used to define neurological function in other studies [2, 3, 8], a final sensitivity analysis was performed defining LND as an increase of NIHSS score ≥ 4 points or death during the period from 48 h to 1 week after symptom onset. In this analysis, LND occurred in 37.3 % (41/110) patients with NIHSS score records available, and it remained associated with unfavorable outcome (OR = 3.410, 95 % CI 1.045–11.126, $p = 0.042$) after adjusting for ICH score.

Discussion

The major findings of this study include identification of a relatively high incidence of LND, an association of LND with unfavorable outcome, and a set of predictors of LND (hematoma volume, IVH, and GLU). With an incidence rate of 28.9 % in this study population, LND may not be a rare phenomenon after ICH. Identifying the incidence of and a set of predictors for LND may provide information regarding the evolution of the disease course to clinicians, patients, and their families. More informed decision-making may lead to triage of patients at high risk of LND to facilities with specialized neurological intensive care [5]. Further, in the present study, 83.7 % of LND (36/43) occurred between day 3 and 5; thus, these results may advocate a LOS of 5 days in NICU for patients at high risk of LND.

Compared to ischemic stroke and subarachnoid hemorrhage, ICH is the least treatable form of stroke. Recently, several large clinical trials, such as FAST [9], INTERACT [10], and STICH [11], focused on management of patients in acute phase of ICH with strict therapeutic windows, but no effective treatment has been confirmed to improve patient outcome. However, potential targets for future therapeutic intervention of ICH may come from preclinical research of secondary injury mechanisms. These studies suggest that secondary neurological damage may result from thrombin production, coagulation cascades, erythrocyte lysis, and hemoglobin toxicity after ICH [12–14]. This pathophysiology may result in the clinical appearance of LND. Independent association between LND and clinical outcome implies the potential importance of inhibiting delayed brain injury after ICH. However, only one study to date has examined LND in patients with ICH and reported an incidence of 13.3 % between Day 3 and Day 6 after symptom onset [4]. The relatively small sample size ($n = 45$) and restriction to non-comatose ICH patients may contribute to the lower risk of neurological worsening compared to the present study [4].

In the present study, hematoma volume, IVH, and GLU on admission were independent predictors of LND, and may correctly classify up to 73 % of patients with subsequent LND. Hematoma volume is a key factor affecting outcome after ICH [15]. LND appears to be

associated with larger hematoma volume. Previous studies described the dose effect of blood components and degradation products on secondary brain injury after ICH [16–18]. This may explain the association between hematoma volume and LND. IVH has been previously shown to have similar associations with mortality, poor functional outcome, and early neurological deterioration in patients with ICH [2, 19–21]. In the present study population, IVH was associated with a 2.5-fold increase in the risk of LND. Possible mechanisms include damage to periventricular brain structures, hydrocephalus, and IVH-induced neuroinflammatory response [19]. Approximately 60 % of patients develop hyperglycemia in the early stages after ICH [22, 23]. Although the proportion of patients with previous history of diabetes was similar between the patients with LND and those without, GLU remained an independent predictor of LND in the present multivariate analysis. Further, after controlling for other poor prognostic indicators, increased GLU remained independently associated with worse functional outcome and early death [24, 25]. Abnormal intracellular calcium recovery due to hyperglycemia is advocated as a cause for GLU effect on neurological damage after ICH [24, 26].

In the present study population, increase in MLS was found to have an independent association with LND after adjusting for hematoma volume, IVH, and GLU on admission. MLS is considered a surrogate measure for cerebral edema [5, 27]; thus, the development of perihematoma edema may be a possible mechanism for LND after ICH. The effect of perihematoma edema on clinical outcome is somewhat controversial with [16, 27] and without [18, 28] associations with mortality. While those studies measured perihematoma edema <72 h after ICH onset, the present study analyzed the progression of brain edema at a median of 4.8 days between symptom onset and follow-up CT scan. As brain edema increases within the first week after ICH [16, 17, 27], the present results may better reflect the clinical significance of perihematoma edema. However, cerebral edema was analyzed in a subgroup of patients with available follow-up CT imaging, which may limit the impact of the present findings.

In this study, GCS was used to define LND due to its high inter-observer reliability [29, 30]. While the definition of LND remains consistent with previous studies that have evaluated in-hospital deterioration among patients with ICH [4, 30], there are no gold standard criteria for LND after ICH. Further, use of the NIHSS in a sensitivity analysis did not affect the findings.

There are several limitations to the present study that should be addressed. First, enrollment from a single quaternary care hospital may limit the generalizability of these results. Second, the incidence rate of LND may be underestimated due to early discharge prior to 1 week after ICH onset in some patients. A sensitivity analysis in patients with an in-hospital LOS of 1 week or more demonstrated LND incidence of 32.0 %. However, patients with LND had a longer LOS; thus, this sensitivity analysis may overestimate the risk of LND. The actual incidence of LND is likely between the original result of 28.9 and 32.0 %. The relatively narrow range indicates limited bias. Third, trial design did not allow predefined time points for imaging. Previous studies have shown the volume of perihematoma edema and MLS increase gradually within the first week after ICH [16, 17, 27]. While follow-up imaging occurred around 4–5 days after ICH for both groups, the association between MLS

and LND can only be definitively validated through systematic, prospective study. Fourth, because of variability in volumetric assessments of edema, MLS was used as a surrogate evaluation of the progression of brain edema [18, 28, 31, 32]. Although MLS is correlated with volume of brain edema in preclinical models [33], reliable volumetric measurements of perihematoma edema may lead to more refined assessment of its significance. Despite these limitations, given the limited knowledge on LND, the present study remains significant because it provides the first exploratory analysis of the predictors, pathophysiology, and clinical significance of neurological deterioration beyond 48 h after ICH onset. Of course, further prospective multicenter trials are needed to confirm our findings.

Conclusions

Nearly 30 % of patients in this study population with spontaneous supratentorial ICH developed LND. Further, LND is associated with unfavorable outcome. Independent predictors of LND include hematoma volume, IVH, and GLU on admission. The progression of perihematoma edema may be one mechanism for LND. However, the exploratory nature of these data warrants further validation.

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Fig. 1.

Flowchart of study population selection. *DNR* do not resuscitate, *GCS* glasgow coma scale, *ICH* intracerebral hemorrhage, *NICU* neuroscience intensive care unit

Table 1

Comparisons of demographics and clinical characteristics between patients with and without late neurological deterioration

	Total (n = 149)	Patients with LND (n = 43)	Patients without LND (n = 106)	p value
Age (years), median (IQR)	61 (49–74)	65 (52–75)	60 (48–71)	0.281
Male sex, n (%)	80 (53.7)	24 (55.8)	56 (52.8)	0.741
Race, n (%)				
White	64 (43.0)	17 (39.5)	47 (44.3)	0.810
African American	77 (51.7)	24 (55.8)	53 (50.0)	
Other	8 (5.4)	2 (4.7)	6 (5.7)	
Hypertension, n (%)	131 (89.7)	39 (90.7)	92 (86.8)	0.507
Diabetes mellitus, n (%)	35 (23.5)	9 (20.9)	26 (24.5)	0.639
Hyperlipidemia, n (%)	43 (28.9)	14 (32.6)	29 (27.4)	0.526
Previous stroke, n (%)	28 (18.8)	10 (23.3)	18 (17.0)	0.374
Coronaryopathy, n (%)	25 (16.8)	9 (20.9)	16 (15.1)	0.388
Atrial fibrillation, n (%)	7 (4.7)	1 (2.3)	6 (5.7)	0.674
Time from symptom onset to NICU admission (hours), median (IQR)	6.3 (3.8–9.3)	6.2 (3.8–7.7)	6.4 (3.9–11.0)	0.359
Admission SBP (mmHg), median (IQR)	154 (138–173)	154 (135–169)	157 (140–175)	0.596
Admission DBP (mmHg), median (IQR)	76 (66–89)	75 (65–87)	77 (69–89)	0.498
Admission temperature (°C), median (IQR)	36.7 (34.4–37.0)	36.6 (36.2–37.0)	36.8 (36.4–37.0)	0.339
Admission GCS score, median (IQR)	13 (7–15)	9 (6–14)	14 (8–15)	<0.001
Admission WBC ($\times 10^9/L$), median (IQR)	9.1 (7.4–12.0)	10.7 (8.5–13.1)	8.8 (7.1–11.7)	0.024
Admission platelet count ($\times 10^9/L$), median (IQR)	230 (186–270)	220 (184–253)	233 (185–277)	0.415
Admission GLU (mg/dl), median (IQR)	129 (108–163)	156 (123–202)	117.5 (106–153)	<0.001
Time from symptom onset to admission CT (hours), median (IQR)	3.8 (1.3–8.8)	3.5 (1.2–7.1)	3.9 (1.4–9.0)	0.286
Hematoma location, n (%)				
Lobar	62 (41.6)	17 (39.5)	45 (42.5)	0.743
Deep	87 (58.4)	26 (60.5)	61 (57.5)	
IVH, n (%)	64 (43.0)	27 (62.8)	37 (34.9)	0.002
Hematoma volume ^a (ml), median (IQR)	18.8 (7.2–42.5)	44.4 (8.3–65.5)	14.7 (6.6–33.0)	0.002
MLS (mm), median (IQR)	2.0 (0–4.3)	3.4 (0–7.0)	0 (0–4.0)	0.016

CT computed tomography, °C degrees Celsius, DBP diastolic blood pressure, dl deciliter, GCS glasgow coma scale, GLU serum glucose, IQR interquartile range, IVH intraventricular hemorrhage, l liter, ml milliliter, MLS midline shift; mg milligram, mm millimeter, n number, NICU neuroscience intensive care unit, SBP systolic blood pressure, WBC white blood cell count

^aIn 43 patients with and 103 patients without LND

Table 2

Predictors of late neurological deterioration in multivariate analysis

Predictors	Odds ratio (95 % CI)	<i>p</i> value
Hematoma volume (ml)	1.017 (1.003–1.032)	0.019
Intraventricular hemorrhage	2.519 (1.142–5.554)	0.022
Serum glucose (>140 vs. 140 mg/dl)	2.614 (1.146–5.965)	0.022

43 patients with LND and 103 patients without LND were included in this logistic regression model. Age, gender, admission white blood cell count, admission Glasgow Coma Scale score, midline shift on admission brain computed tomography images were included in the stepwise regression, but did not reach statistically significant relationships with late neurological deterioration after controlling for the covariates

Table 3

Comparisons of hematoma expansion and midline shift increase in patients with follow-up computed tomography imaging

	Patients with LND (<i>n</i> = 25)	Patients without LND (<i>n</i> = 40)	<i>p</i> value
Interval from symptom onset to follow-up CT (days), median (IQR)	4.0 (3.1–6.2)	5.6 (3.8–6.4)	0.103
Hematoma expansion ^a , <i>n</i> (%)	3 (12.0)	4 (10.8)	1.000
MLS increase, <i>n</i> (%)	12 (48.0)	8 (20.0)	0.017

CT computed tomography, LND late neurological deterioration, MLS midline shift, *n* number

^aIn 25 patients with and in 37 patients without late neurological deterioration