Original Contribution

Time Course and Predictors of Neurological Deterioration After Intracerebral Hemorrhage

Aaron S. Lord, MD; Emily Gilmore, MD; H. Alex Choi, MD; Stephan A. Mayer, MD; on behalf of VISTA-ICH Collaboration*

Background and Purpose—Neurological deterioration (ND) is a devastating complication after intracerebral hemorrhage but little is known about time course and predictors.

Methods—We performed a retrospective cohort study of placebo patients in intracerebral hemorrhage trials. We performed computed tomographic scans within 3 hours of symptoms and at 24 and 72 hours; and clinical evaluations at baseline, 1-hour, and days 1, 2, 3, and 15. Timing of ND was predefined as follows: hyperacute (within 1 hour), acute (1–24 hours), subacute (1–3 days), and delayed (3–15 days).

Results—We enrolled 376 patients and 176 (47%) had ND within 15 days. In multivariate analyses of ND by category, hyperacute ND was associated with hematoma expansion (odds ratio [OR], 3.6; 95% confidence interval [CI], 1.7–7.6) and baseline intracerebral hemorrhage volume (OR, 1.04 per mL; 95% CI 1.02–1.06); acute ND with hematoma expansion (OR, 7.59; 95% CI, 3.91–14.74), baseline intracerebral hemorrhage volume (OR, 1.02 per mL; 95% CI, 1.01–1.04), admission Glasgow Coma Scale (OR, 0.77 per point; 95% CI, 0.65–0.91), and interventricular hemorrhage (OR, 2.14; 95% CI, 1.05–4.35); subacute ND with 72-hour edema (OR, 1.03 per mL; 95% CI, 1.02–1.05) and fever (OR, 2.49; 95% CI, 1.01–6.14); and delayed ND with age (OR, 1.11 per year; 95% CI, 1.04–1.18), troponin (OR, 4.30 per point; 95% CI, 1.71–10.77), and infections (OR, 3.69; 95% CI, 1.11–12.23). Patients with ND had worse 90-day modified Rankin scores (5 versus 3; P<0.001).

Conclusions—ND occurs frequently and predicts poor outcomes. Our results implicate hematoma expansion and interventricular hemorrhage in early ND, and cerebral edema, fever, and medical complications in later ND. (Stroke. 2015;46:00-00. DOI: 10.1161/STROKEAHA.114.007704.)

Key Words: cerebral hemorrhage • Glasgow Coma Scale • neurological disorders

Neurological deterioration (ND) is a devastating complication after spontaneous intracerebral hemorrhage (ICH) that occurs in 8% to 33% of patients.1–4 Retrospective and registry data have shown an association between ND and large hematoma volumes (>45–60 mL), especially when mass effect and midline shift are present.3,4 Although a study demonstrated ND to be associated with admission Glasgow Coma Scale (GCS) scores of <14,4 another study could not confirm this association.5

Apart from large ICH volume, which presumably drives worsening because of infarction, mass effect, and brain tissue shifts, early hematoma expansion has been implicated as the cause of hyperacute ND in ≤25% of patients.3 Clinical factors associated with hematoma growth, such as elevated systolic blood pressure or presence of a spot-sign, have also been associated with ND.1,6

Leira et al2 reported the largest prospective study examining ND after ICH.2 In their study of 261 patients with noncomatose ICH presenting within 12 hours of ictus, ND occurred in 22% of patients within 48 hours of hospitalization. Admission characteristics associated with ND included interventricular hemorrhage (IVH), temperature >37.5°C, increased neutrophil count, and increased fibrinogen levels. Hematoma expansion and severe hypertension occurring within 48 hours of admission were also associated with ND.

ND occurs most frequently within the first 24 hours of hospital admission, and a large proportion of these cases occur within the first 6 to 12 hours of hemorrhage onset.3,6 More precise understanding of the time course and risk factors of ND during the hyperacute stage of ICH has been lacking because of enrollment windows of prior studies that have extended from 12 to 24 hours after symptom onset.2,3 Using the Virtual International Stroke Trials Archive (VISTA) database, we studied the time course and identified radiological correlates of ND in a large cohort of patients with ICH who underwent computed tomographic (CT) imaging within 3 hours of ICH onset.

Received October 16, 2014; final revision received December 10, 2014; accepted December 22, 2014.

From the Division of Neurocritical Care, Department of Neurology, New York University School of Medicine (A.S.L.); Division of Neurocritical Care, Department of Neurology, Yale University School of Medicine (E.G.); Division of Neurocritical Care, Department of Neurology, University of Texas, Houston (H.A.C.); and Institute of Critical Care Medicine, Icahn School of Medicine at Mount Sinai, NY (S.A.M.).

*A list of all VISTA-ICH Steering Committee members is given in the Appendix.

Correspondence to Aaron S. Lord, MD, 530 1st Ave, Suite 5A, NY, NY 10016. E-mail Aaron.Lord@Nyumc.org

© 2015 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.114.007704
Methods
Study Design and Population
We performed a retrospective cohort study of patients enrolled in the VISTA database who were enrolled in the placebo arm of prospective, randomized clinical trials of acute treatments for ICH. Our primary aim was to determine the incidence of ND at distinct time points after admission with ICH and to determine clinical and radiographic features associated with deterioration at each time point. We hypothesized that early ND would be associated with large initial ICH volumes and hematoma expansion, and later ND would be associated with edema formation and intraventricular hemorrhage.

Inclusion criteria included baseline CT scan performed within 3 hours of symptom onset, follow-up CT scan at 24 and 72 hours, and GCS and National Institutes of Health Stroke Scale (NIHSS) performed at baseline, 1 hour, 1 day, 2 days, 3 days, and 15 days, and available 3-month modified Rankin Scale score. Exclusion criteria included administration of an active investigational drug, presenting GCS of ≤5, surgical evacuation of hematoma planned within 24 hours, secondary ICH, and known anticoagulation therapy or coagulopathy. Additional methods and exclusion criteria about these studies have been previously reported.8,9

Definitions
ND was defined as a ≥2 point decrease in GCS or a ≥4 point increase in the NIHSS score. We examined the time course of ND based on the following predefined periods and on timing of available clinical evaluations:

1. Hyperacute deterioration (HD; 0–1 hours)
2. Acute deterioration (AD; 1–24 hours)
3. Subacute deterioration (1–3 days)
4. Delayed deterioration (3–15 days)

HD compared baseline and 1-hour scores. Clinical scores at other time points compared clinical scores at the beginning and end of the time period. In addition, we created 2 additional categories for analysis purposes: (1) no deterioration group (NoD) who had stable or improving GCS during each period throughout the first 15 days; and (2) any deterioration group consisting of all patients experiencing deterioration in any of the predefined time periods as well as those who experienced a gradual decline across multiple time periods compared with baseline (eg, a 2-point NIHSS increase in the hyperacute period and another 2-point NIHSS increase in the acute period). Given the aim of the study was to identify drivers of ND at specific time points, subjects experiencing a gradual decline in their examination were not included in a specific individual deterioration group but were included in the “Any Deterioration” group. Hematoma expansion was defined as an increase of ICH volume on follow-up CT scans of either 6 mL or >33%.

Statistical Analysis
Univariate and multivariate analyses were performed to identify demographic, clinical, and radiographic predictors of deterioration for each subgroup using χ² test, Fisher Exact Test, Mann–Whitney U test, and logistic regression as appropriate. Each subgroup was compared with the pool of patients who did not experience ND during the study (NoD group). Kaplan–Meier survival analysis was performed to test effect of clinical variables on ND-free survival. All statistical analysis was performed on commercially available software (IBM SPSS Statistics 21).

Results
Baseline Characteristics
We enrolled 376 patients with ICH into the study (Table 1). Overall, the subjects experienced mild-moderate illness, with a median GCS of 14, NIHSS of 14, and ICH volume of 14 mL. Eight patients underwent surgical hematoma evacuation that had not been planned at the time of enrollment. ND occurred in 176 (47%) patients at any point during the study, 170 at discrete time points, and 6 gradually during multiple time periods. The first episode of ND was most likely to occur within the first 24 hours (123/176, 70%), and one third of these patients deteriorated within the first hour (42/123, 34%). Compared with those with NoD at any point during the study, patients with hyperacute and acute ND were more likely to have lower GCS (HD, AD versus NoD: 14, 13 versus 15; P=0.003; P<0.001), higher NIHSS (HD, AD versus NoD: 15, 16 versus 12; P=0.02; P<0.001), larger hematoma volumes (HD, AD versus NoD: 23, 24 versus 9 mL; both P<0.001), and presence of IVH (HD, AD versus NoD: 43%, 38% versus 25%; both P=0.02). Patients with acute ND were more likely to have a lobar location of their hematoma (AD versus NoD: 24% versus 10%; P=0.002) and had higher serum glucose (AD versus NoD: 129 versus 114; P=0.01). Patients with subacute ND shared many characteristics with patients with hyperacute and acute ND, although increased rates of fever (subacute deterioration versus NoD, 38% versus 15%; P=0.003) and higher IVH blood volumes (subacute deterioration versus NoD; median 0, IQR 0–3.0 mL versus median 0, IQR 0–0 mL; P=0.006) were unique associations in this group.

ND-Free Survival Curves
Figure 1 demonstrates a Kaplan–Meier curve of ND-free survival in all patients (Figure 1A) and by admission ICH-volume strata (Figure 1B). Of those patients who did not experience ND by 72 hours, only 6% went on to have delayed ND by day 15. For those with ND in the first 72 hours, 22% had further delayed ND.

CT Characteristics
Characteristics of baseline, 24-hour, and 72-hour CT scans are reported in Table 2. Both HD and AD were associated with hematoma expansion from baseline to 24-hour scans compared with the NoD group (HD, AD versus NoD; 46%, 63% versus 20%; both P<0.001). Patients with ND in the first 24 hours had higher volumes of hematoma expansion (11 versus 1 mL; P<0.001). Hematoma expansion was not associated with subacute ND. Although median IVH volumes were 0 at baseline and 24 hours in both groups, there was a significant increase in IVH volumes in those with ND in the first 24 hours. Increased IVH volumes on 24-hour and 72-hour scans were associated with subacute deterioration. Edema volume was not associated with ND in the first 24 hours, but volume of edema at 72 hours (43 versus 18 mL; P<0.001) were associated with subacute ND.

Multivariable Model for ND
In multivariate analyses of ND within predefined categories, hyperacute ND was associated with hematoma expansion (odds ratio [OR], 3.6; 95% confidence interval [CI], 1.7–7.6) and baseline ICH volume (OR, 1.04 per mL; 95% CI, 1.02–1.06); acute ND with hematoma expansion (OR, 7.59; 95% CI, 3.91–14.74), baseline ICH volume (OR, 1.02 per mL;


### Table 1. Patient Characteristics by Neurological Deterioration Status

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Yes Neurological Deterioration</th>
<th>No Neurological Deterioration</th>
<th>P Value</th>
<th>Hyperacute (N=42)</th>
<th>First Neurological Deterioration by Category vs No Deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (± SD)</td>
<td>68 (±14)</td>
<td>64 (±12)</td>
<td>0.003</td>
<td>66 (±14)</td>
<td>0.3</td>
</tr>
<tr>
<td>Women</td>
<td>73 (42%)</td>
<td>73 (37%)</td>
<td>0.3</td>
<td>20 (48%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Non-White</td>
<td>44 (25%)</td>
<td>63 (32%)</td>
<td>0.2</td>
<td>12 (29%)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**Admission clinical scores**

- Baseline GCS: 14 (11–15) vs 15 (14–15); <0.001
- Baseline NIHSS: 16 (12–19) vs 12 (7–16); <0.001

**Admission vitals**

- Systolic BP, mmHg: 180 (160–200) vs 177 (157–194); 0.2
- Diastolic BP, mmHg: 95 (80–110) vs 97 (84–110); 0.4
- Temperature, °C: 36.3 vs 36.5; 0.05*
- Alcohol use: 15 (99) vs 15 (103); 0.7
- Hypertension: 25 (14%) vs 42 (22%); 0.07
- Diabetes mellitus: 2 (1%) vs 5 (3%); 0.4
- Hyperlipidemia: 18 (10%) vs 26 (13%); 0.4
- Tobacco use: 16 (9%) vs 23 (12%); 0.7
- Alcohol use: 15 (9%) vs 15 (9%); 0.7

**Admission radiographic data**

- ICH volume, mL: 23.4 (9.9–46.6) vs 24.4 (8.7–49.2); <0.001
- IVH present: 78 (44%) vs 49 (25%); <0.001
- ICH volume, mL: 0 (0–110) vs 0.5 (0–110); 0.7
- Edema volume, mL: 4.9 (0–21.9) vs 4.7 (0–14.8); 0.05*
- Total blood volume, mL: 25.7 (13.0–52.7) vs 24.9 (15.9–55.7); <0.001
- Lobar location: 30 (17%) vs 6 (14%); 0.03
- Infratentorial location: 10 (6%) vs 2 (5%); 0.9

**Past medical history**

- Hypertension: 25 (14%) vs 42 (22%); 0.07
- Diabetes mellitus: 2 (1%) vs 5 (3%); 0.4
- Hyperlipidemia: 18 (10%) vs 26 (13%); 0.4
- Tobacco use: 16 (9%) vs 23 (12%); 0.7
- Alcohol use: 15 (9%) vs 15 (9%); 0.7

**Admission laboratory values**

- Glucose, mg/dL: 124 (119–145) vs 129 (105–158); 0.04
- Creatinine, mg/dL: 1.0 (0.8–1.3) vs 0.9 (0.8–1.2); 0.6
- Sodium, mmol/L: 139 (137–141) vs 140 (138–142); 0.9
- INR: 1.0 (0.9–1.2) vs 1.0 (0.9–1.1); 0.6
- aPTT, s: 29.0 (26.3–33.1) vs 29.0 (26.3–33.1); 0.2
- Troponin, µg/L: 0.1 vs 0.05; 0.002
- Cholesterol, mmol/L: 5.0 (4.0–5.6) vs 4.7 (3.9–5.6); 0.5
- Fibrin, g/L: 4.0 (3.1–4.8) vs 3.5 (2.6–4.3); 0.2
- Factor 1+2, mmol/L: 1.0 (0.6–1.5) vs 0.9 (0.5–1.4); 0.001

Categorical variables are noted as % (N). Continuous variables are as noted. Continuous variables are in the units noted followed by either ± SD or interquartile range. aPTT indicates activated partial thromboplastin time; BP, blood pressure; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; INR, international normalized ratio; IVH, intraventricular hemorrhage; and NIHSS, National Institutes of Health Stroke Scale.

*Nonsignificant P value before rounding.
Outcomes

Three-month outcomes are listed in Table 3. Patients with ND at any point in the study were more likely to die (42% versus 3%; \( P < 0.001 \)) and have lower median modified Rankin Scale (5 versus 3; \( P < 0.001 \)). Of the 5 patients who died between day 15 and 90, 3 died from medical complications, 1 from a fall, and another because of progression of neurological deficits. Breakdown of modified Rankin Scale stratifying for ND can be seen in Figure 2.

Discussion

We found that when the initial clinical evaluation is performed within 3 hours of onset, ND after ICH is common: almost half of patients will clinically worsen at some point during their first 15 days of hospitalization. Interestingly, deterioration is not a complication reserved just for patients with large bleeds or poor clinical presentations. The median admission GCS for those experiencing ND at any point in the first 15 days was 14 and median ICH size was 23 mL. We also found a striking association between ND and poor outcome. Patients who deteriorate are more likely to have further worsening during their hospitalization, and mortality occurs almost exclusively among patients who have worsened. Clinical strategies focused on prevention of ND are a logical step for improving outcome after ICH.

Table 2. Computed Tomography Dynamics

<table>
<thead>
<tr>
<th></th>
<th>Hyperacute or Acute ND</th>
<th>Subacute ND</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>ICH volume, mL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission scan volume</td>
<td>24 (9–49)</td>
<td>9 (5–20)</td>
</tr>
<tr>
<td>24-Hour scan volume</td>
<td>37 (12–70)</td>
<td>11 (5–24)</td>
</tr>
<tr>
<td>Median change</td>
<td>11 (0–24)</td>
<td>1 (0–2)</td>
</tr>
<tr>
<td><strong>ICH volume, mL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission scan volume</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>24-Hour scan volume</td>
<td>0 (0–5)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>Median change</td>
<td>0 (0–4)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td><strong>Edema volume, mL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission scan volume</td>
<td>6 (0–22)</td>
<td>4 (0–11)</td>
</tr>
<tr>
<td>24-Hour scan volume</td>
<td>12 (0–51)</td>
<td>10 (3–22)</td>
</tr>
<tr>
<td>Median change</td>
<td>4 (0–27)</td>
<td>3 (0–9)</td>
</tr>
</tbody>
</table>

All volumes are in mL and presented as medians (interquartile range). ICH indicates intracerebral hemorrhage; IVH, interventricular hemorrhage; and ND, neurological deterioration.
What are the drivers leading patients to worsen at different points during their hospitalization? We confirmed prior studies demonstrating that ND within 24 hours of onset is driven primarily by the amount of blood, including acute hematoma expansion. We also found that IVH is a significant driver of AD, likely because of multiple factors, including neurotoxicity of blood products, especially on the diencephalon, and hydrocephalus. Patients who worsened between 24 and 72 hours had large edema volumes and subacute fevers, pointing to these entities as drivers of deterioration during this time period. Delayed worsening between days 3 and 15 was seen in patients with increased age, troponin levels, and infectious complications, suggesting that medical complications and lack of functional reserve may be driving delayed deterioration. However, causation in this time period is difficult to assess because medical complications could also arise as a result of long hospital stays in those with ND.

There are weaknesses to this study. Most importantly, patients in this study need to meet stringent enrollment criteria for participation in phase II and III randomized-controlled trials and had to consent to participation. Therefore, our study population is biased toward less disease severity than the ICH population at large. There was not a standardized way to account for residual effect of anesthetic agents in the follow-up clinical assessments of 8 patients who underwent hematoma evacuation. Although they are included in the final analysis, their exclusion did not meaningfully change the multivariate models. In addition, although we defined the hyperacute period as being the first hour after enrollment, our inclusion criteria allowed enrollment of patients for ≤3-hour postictus. Thus, the exact postictus timing of the hyperacute period varied depending on when the patient presented and was enrolled. There are also considerable strengths to this study. It is multicenter, with prospective data collection at pre-established time points, and with 5 clinical assessments and 3 CTs within the first 72 hours.

Our study has clinical implications. In practice, we should prepare families—who often expect patients to improve rather than worsen after hospitalization—these chances are equally likely for worsening because they are for stability or improvement. This is true for patients with even moderate size hemorrhages and decent initial clinical exams. Conversely, lack of deterioration is a favorable finding and implies a favorable long-term prognosis.

ND remains a common and devastating complication after ICH. Although some risk factors are not modifiable, others, including hematoma expansion in the first 24 hours and edema volume and fever in the subacute period, are amenable to treatment. Given the deleterious impact on outcomes, we

<table>
<thead>
<tr>
<th>Neurological Worsening in Study</th>
<th>Yes</th>
<th>No</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td>74 (42%)</td>
<td>5 (3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mRS</td>
<td>5 (4–6)</td>
<td>3 (1–4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Barthel</td>
<td>8 (0–50)</td>
<td>90 (65–100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NIHSS</td>
<td>14 (6–32)</td>
<td>3 (1–6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>European QOL</td>
<td>0.12 (0.00–0.71)</td>
<td>0.76 (0.42–0.83)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and QOL, quality of life.
should continue to search for treatments which prevent hematoma expansion, edema formation, and fever to reduce the impact of ND on outcomes. Further trials focused on arresting early hematoma growth with hemostatic therapy are justified, as are trials of medical and surgical interventions for reducing compartmentalized mass effect and tissue shifts.

Appendix

VISTA-ICH Steering Committee

Disclosures
None.

Sources of Funding
Dr Lord received support from the New York University-Health and Hospitals Corporation Clinical and Translational Science Institute via grant UL1 TR000038 from the National Center for Advancing Translational Sciences of the National Institutes of Health.

References
Time Course and Predictors of Neurological Deterioration After Intracerebral Hemorrhage
Aaron S. Lord, Emily Gilmore, H. Alex Choi and Stephan A. Mayer on behalf of VISTA-ICH Collaboration

Stroke. published online February 5, 2015;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2015/02/05/STROKEAHA.114.007704