Monocyte Count and 30-Day Case Fatality in Intracerebral Hemorrhage

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**Background and Purpose**—Monocytes may contribute to secondary injury after intracerebral hemorrhage (ICH). We tested the association of absolute monocyte count with 30-day ICH case fatality in a multiethnic cohort.

**Methods**—Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study is a prospective, multicenter, case–control study of ICH among white, black, and Hispanic patients. In 240 adults with nontraumatic ICH within 24 hours of symptom onset, we evaluated the influence of ICH score and complete blood count components on 30-day case fatality using generalized linear models.

**Results**—Mean age was 62.8 years (SD, 14 years); 61.7% were men, 33.3% black, and 29.6% Hispanic. Median ICH volume was 9.9 mL (interquartile range, 4.4–26.7). After adjusting for patient age and initial hemoglobin, higher total white blood cell count ($P=0.0011$), driven by higher absolute neutrophil count ($P=0.002$), was associated with larger ICH volume, whereas absolute monocyte count was not ($P=0.15$). After adjusting for age, Glasgow Coma Scale, ICH volume, location, and the presence or absence of intraventricular hemorrhage, baseline absolute monocyte count was independently associated with higher 30-day case-fatality (odds ratio, 5.39; 95% confidence interval, 1.87–15.49; $P=0.0018$), whereas absolute neutrophil count (odds ratio, 1.04; 0.46–2.32; $P=0.93$) and white blood cell count (odds ratio, 1.62; 0.58–4.54; $P=0.36$) were not.

**Conclusions**—These data support an independent association between higher admission absolute monocyte count and 30-day case-fatality in ICH. Inquiry into monocyte-mediated pathways of inflammation and apoptosis may elucidate the basis for the observed association and may be targets for ICH neuroprotection. (Stroke. 2015;46:2302-2304. DOI: 10.1161/STROKEAHA.115.009880.)

**Key Words:** cerebral hemorrhage ■ Glasgow Coma Scale ■ inflammation ■ monocytes ■ odds ratio

Intracerebral hemorrhage (ICH) accounts for 10% of all strokes but 50% of stroke mortality. No therapies have shown definitive benefit after ICH. Infiltrating white blood cells (WBCs) play a role in secondary injury after ICH. In clinical studies, WBC count has been associated with larger ICH volume, early neurological deterioration, and worse discharge disposition. However, the individual contributions of leukocyte cell types remain unclear.

In a murine ICH study, circulating inflammatory monocytes outnumbered other leukocytes in brain tissue, and mice with fewer inflammatory monocytes had better motor function. Limiting monocyte recruitment into brain tissue after ICH also resulted in less neurobehavioral disability. A clinical study of 85 ICH patients found that higher serum monocyte chemoattractant protein-1, the dominant chemokine for monocyte recruitment, at 24 hours was independently associated with worse modified Rankin Scale at 7 days. Based on these data, we recently investigated associations between absolute monocyte count (AMC), ICH volume, and 30-day fatality in 186 ICH patients who presented within 12 hours of symptom onset. AMC was not associated with ICH volume, but was independently associated with case-fatality. In the present study, we seek to confirm our prior findings using a cohort independent of the discovery set of ICH patients in a multiethnic, multicenter study, by determining the association of WBC count, absolute neutrophil count (ANC), and AMC with baseline ICH volume and 30-day case-fatality.

**Methods**
Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study is a prospective, multicenter, case–control study of ICH among white, black, and Hispanic patients. The methods of the ERICH study have
Table 1. Characteristics of Included Ethnic/Racial Variations of Intracerebral Hemorrhage Patients

<table>
<thead>
<tr>
<th>Race categories, n (%)</th>
<th>White</th>
<th>Hispanic</th>
<th>Black</th>
<th>Non-Hispanic white</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>89</td>
<td>71</td>
<td>80</td>
<td>240</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>62.8</td>
<td>71.2</td>
<td>62.5</td>
<td>62.8 (14.0)</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>148 (61.7)</td>
<td>71 (29.6)</td>
<td>80 (33.3)</td>
<td>240</td>
</tr>
</tbody>
</table>

Results

Table 1 shows the characteristics of included patients. After adjusting for patient age and initial hemoglobin, higher total WBC count ($P=0.0011$), driven by higher ANC ($P=0.002$), was associated with larger ICH volume, whereas AMC was not ($P=0.15$; Table 2). Odds ratios for 30-day case-fatality were determined after adjusting for age, Glasgow Coma Scale, ICH volume, ICH location, and the presence or absence of intraventricular hemorrhage. Higher baseline AMC was independently associated with 30-day case-fatality (odds ratio, 5.39; 95% confidence interval, 1.87–15.49; $P=0.0018$), whereas ANC (odds ratio, 1.04; 0.46–2.32; $P=0.93$) and total WBC count (odds ratio, 1.62; 0.58–4.54; $P=0.36$) were not (Table 3).

Discussion

We confirmed an independent association of AMC with 30-day ICH case-fatality after adjusting for important confounders. Our present findings are consistent with prior data. Associations of higher WBC count and ANC with ICH volume have been reported by other investigators, but likely represent an acute phase response. Our initial report was the first to suggest an independent role for monocytes. Confirming those findings provides additional support for the concept of monocytes specifically contributing to secondary injury after ICH. Proposed mechanisms include damage to the blood–brain barrier, binding to chemotactic proteins in cerebral vessels that promotes neuronal death and cell injury, and contribution to cerebral edema.

The therapeutic implication of our findings is that monocyte inflammatory pathways may be targets for neuroprotection in ICH. Preclinical models suggest that monocyte depletion, reduction in monocyte recruitment to the site of ICH, and targeted antibodies to reduce monocyte infiltration may all result in improved functional outcome after ICH. Our findings provide justification for well-designed preclinical and early phase clinical studies investigating the inhibition of inflammatory monocytes in ICH. In ischemic stroke, preclinical evidence has led to a clinical study investigating natalizumab, a monoclonal antibody that blocks leukocyte adhesion to endothelial cells and is approved for the treatment of multiple sclerosis, for reducing infarct size. Thus, natalizumab or similar agents may be candidates for preclinical and clinical studies in ICH. Recent data also suggest the interaction of initial monocyte expansion and subsequent suppression via the HMGB1-RAGE (high mobility group box 1–receptor for advanced glycation end products) pathway may influence observed outcomes in ischemic stroke. This line of inquiry may further elucidate targets for intervention.

Limitations of our study include its retrospective nature, inability to investigate temporal trends in cell counts, and lack of follow-up imaging data allowing for investigation of the association of leukocyte counts and hematoma expansion. Our prior report found no association of AMC with hematoma expansion.

Conclusions

Our findings complement a growing body of evidence from clinical and preclinical investigations supporting a unique role...
of monocytes in secondary neuroinflammatory injury after ICH. Inhibitors of monocyte migration and activity may be novel therapeutic targets for ICH.

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Disclosures
None.

References

Table 3. Association of Leukocyte Counts With 30-Day Case Fatality

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Total WBC (Log)</th>
<th>Neutrophils (Log)</th>
<th>Monocytes (Log)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Unadjusted</td>
<td>Adjusted*</td>
<td></td>
</tr>
<tr>
<td>GCS</td>
<td>1.09 (1.05–1.14)</td>
<td>1.09 (1.05–1.14)</td>
<td>1.11 (1.06–1.16)</td>
</tr>
<tr>
<td>Location: deep</td>
<td>7.7 (2.0–30.2)</td>
<td>7.3 (1.9–28.3)</td>
<td>10.2 (2.5–41.5)</td>
</tr>
<tr>
<td>Location: infratentorial</td>
<td>11.7 (1.7–80.1)</td>
<td>13.0 (1.9–88.9)</td>
<td>13.7 (1.8–104.7)</td>
</tr>
<tr>
<td>Presence of IVH</td>
<td>0.5 (0.2–1.5)</td>
<td>0.24</td>
<td>0.24</td>
</tr>
</tbody>
</table>

*Adjusted for age, GCS, intracerebral hemorrhage volume, location, and presence of IVH.

CI indicates confidence interval; GCS, Glasgow Coma Scale; IVH, intraventricular hemorrhage; OR, odds ratio; and WBC, white blood cell count.
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