Cerebral Atrophy is an Independent Risk Factor for Unfavorable Outcome After Spontaneous Supratentorial Intracerebral Hemorrhage

Christian Herweh, MD*; Eric Prager, MD*; Marek Sykora, MD; Martin Bendszus, MD

Background and Purpose—To investigate the influence of cerebral atrophy on clinical outcome in patients with supratentorial intracerebral hemorrhage.

Methods—Computed tomography scans of 320 patients included in a prospective, multicenter trial were used for a segmentation analysis to determine the supratentorial cerebral volume. A logistic regression analysis was used to explore its effect on outcome after 90 days in addition to other clinical and imaging parameters.

Results—Cerebral volume loss significantly reduced the odds for favorable outcome after 90 days (odds ratio=0.91; confidence interval, 0.85–0.99; P=0.02).

Conclusions—Cerebral atrophy is an independent predictor of unfavorable outcome after intracerebral hemorrhage, indicating reduced functional recovery potential in these individuals. (Stroke. 2013;44:968-971.)

Key Words: cerebral atrophy ■ computed tomography ■ intracerebral hemorrhage ■ intracranial hemorrhage ■ outcomes

Cerebral atrophy has been shown to be a protective factor in large supratentorial ischemic strokes.1-4 To date, there are no data on the role of cerebral atrophy in spontaneous intracerebral hemorrhage (ICH). This might be of interest because ICH, including the perihematomal edema, exerts similar space-occupying effects. In the present study, we aimed to investigate the influence of relative cerebral volume (RCV) on outcome after supratentorial ICH.

Methods
We used initial computed tomography (CT) scans of patients included in the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial, which has been reported in detail previously.5 In brief, 841 patients with acute spontaneous ICH were included in the trial and were randomized to receive either placebo or hemostatic therapy. CT scans were performed within 3 hours from onset of symptoms. Patients were excluded if they had an initial Glasgow coma scale (GCS) score <6 or a premorbid modified Rankin scale score (mRs) >2. Informed consent from patients or their next of kin was obtained in the primary trial, which was also approved by local institutional review boards and national regulatory authorities as applicable. In the present volumetric analysis, the posterior fossa in general and those with unfavorable outcome. This was done for the whole population as well as in subgroups: <50, 50 to 60, 60 to 70, 70 to 80, and >80 years of age.

The supratentorial brain parenchyma and cerebrospinal fluid spaces as well as the hematoma were segmented using the Analyze software (http://www.mayo.edu/bir/Software/Analyze/Analyze.html) in an approach described previously (Figure 1). The segmentation was repeated with thresholds adjusted to include the corresponding intracranial space. RCV was defined as the volume of the supratentorial brain subtracted by the volume of the hematoma and cerebrospinal fluid spaces divided by the supratentorial intracranial volume. These steps were all performed by a single reader (E.P.). A second reader (C.H.) repeated the procedure independently for every 10th patient being blinded to the initial results, and the inter-reader agreement was calculated. Furthermore, CT scans were evaluated regarding ischemic leukoaraiosis (LA) by a single reader, who used the score introduced by van Swieten et al7 where LA is graded between 0 and 4. This reader also reviewed the CT scans for any other cerebral lesions. Other imaging derived parameters used for the analysis were initial hematoma size as well as the occurrence and amount of intraventricular hemorrhage.

For the statistical analysis, patients’ age, the initial GCS, and mRs at 90 days (mRs 90) were used. Unfavorable outcome was defined as an mRS of >2. In subgroup analysis, we compared patient characteristics between those with favorable and those with unfavorable outcome. This was done for the whole population as well as in subgroups: <50, 50 to 60, 60 to 70, 70 to 80, and >80 years of age.

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Statistical Analysis

Original RCV scaled between 0 and 1 was multiplied by 100 to get percentage counts. For comparison of groups, Student t test, Mann-Whitney U, or the χ2 test was used. The odds for unfavorable outcome or death within 90 days for different predictors were estimated using a multivariate logistic regression analysis. All analyses were performed using a standard software package (Statistical Package for Social Sciences; SPSS, Version 17.0). Level of significance was set to 0.05.

Results

A total of 320 patients had initial CT scans of sufficient quality for the segmentation analysis. There were no signs of older ischemic or hemorrhagic stroke or any other focal brain damage. ICH was located in the basal ganglia in 90% of patients with favorable outcome and in 85% of patients with an unfavorable outcome (P=0.23).

The inter-rater agreement for the calculated RCV values was very good, with a κ of 0.84 (r=0.85; P<0.0001). Patients with an unfavorable outcome were significantly older (67.6 vs 61.3 years; P<0.001), had a lower GCS score on admission (14 vs 15; P<0.001), lower RCV (0.85 vs 0.88; P<0.001), and larger hematoma (18.9 vs 6.5 mL; P<0.001) as well as more severe LA (2 vs 1; P=0.023). RCV showed a negative correlation with patients’ age and LA severity (r=-0.674; P<0.001 and r=-0.297; P=0.01, respectively), but not with hematoma size (Table).

The adjusted odds ratio (OR) for unfavorable outcome at 90 days was significantly higher with increasing ICH volume (OR=1.09; confidence interval [CI], 1.05–1.1; P<0.001) and LA severity (OR=1.25; CI, 1.01–1.54; P=0.04) and was lower with reduced initial GCS score (OR=0.79; CI, 0.63–0.99; P=0.04) and RCV (OR, 0.91; CI, 0.85–0.99; P=0.02; Figure 2). The OR for unfavorable outcome was higher with increasing age (OR, 1.03; CI, 0.99–1.06; P=0.07), which was not significant.

Patients with unfavorable outcome had nonsignificant reductions of RCV in all age subgroups. Only in the youngest (<50 years of age) and oldest (<80 years of age) subgroup, RCV had a significant negative correlation with outcome (r=-0.291; P=0.05 and r=-0.253; P=0.04, respectively).

There was no significant influence of RCV on the OR for survival versus death (P=0.979). The different study arms

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Table. Clinical and Imaging Characteristics in General (n=320) and for Outcome Subgroups

<table>
<thead>
<tr>
<th>Outcome Subgroups</th>
<th>Favorable (mRs&lt;2; n=110)</th>
<th>Unfavorable (mRS&gt;2; n=210)</th>
<th>Level of Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRs 90</td>
<td>3 (0–6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>65.5±13.2</td>
<td>61.3±13.3</td>
<td>67.6±12.7</td>
</tr>
<tr>
<td>RCV</td>
<td>0.86±0.05</td>
<td>0.88±0.04</td>
<td>0.85±0.05</td>
</tr>
<tr>
<td>GCS</td>
<td>15 (7–15)</td>
<td>15 (9–15)</td>
<td>14 (7–15)</td>
</tr>
<tr>
<td>ICH volume</td>
<td>12.8 (0.3–153.4)</td>
<td>6.6 (0.7–77)</td>
<td>18.9 (0.3–153.7)</td>
</tr>
<tr>
<td>IVH</td>
<td>119/320</td>
<td>30/110</td>
<td>89/210</td>
</tr>
<tr>
<td>IVH volume</td>
<td>0 (0–67)</td>
<td>0 (0–25.2)</td>
<td>0 (0–67)</td>
</tr>
<tr>
<td>LA</td>
<td>2 (0–4)</td>
<td>1 (0–4)</td>
<td>2 (0–4)</td>
</tr>
<tr>
<td>Basal ganglia location</td>
<td>278/320</td>
<td>99/110</td>
<td>179/210</td>
</tr>
</tbody>
</table>

GCS indicates Glasgow coma scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; LA, leukoaraiosis; mRs, modified Rankin scale; and RCV, relative cerebral volume.

*Student t test.
†Mann-Whitney U test.
‡χ2 test.
Discussion

The present study investigated the relationship between cerebral volume and clinical outcome after supratentorial ICH. Previous studies identified several factors increasing the risk for poor outcome after ICH, such as age, initial GCS score, initial size of the hematoma, as well as existence and amount of intraventricular hemorrhage. According to that, all these parameters were significantly different between patients with favorable and unfavorable outcomes in the present study. Recently, ischemic LA could be identified as a novel risk factor for unfavorable outcome in ICH after being already recognized as a predictor of poor outcome in ischemic stroke. Using the same score to assess LA, we found it to be significantly more severe in patients with unfavorable outcome. Another risk factor for unfavorable outcome after ischemic stroke is reduced cerebral volume. In the present study, cerebral volume was significantly reduced in patients with unfavorable outcome. As expected, RCV was also negatively correlated with age as well as with the extent of LA. However, a multivariate regression analysis identified cerebral atrophy as an independent predictor of unfavorable outcome. As expected, RCV was also negatively correlated with age as well as with the extent of LA. According to that, all these parameters were significantly different between patients with favorable and unfavorable outcomes in the present study. Recently, ischemic LA could be identified as a novel risk factor for unfavorable outcome in ICH after being already recognized as a predictor of poor outcome in ischemic stroke. Using the same score to assess LA, we found it to be significantly more severe in patients with unfavorable outcome. Another risk factor for unfavorable outcome after ischemic stroke is reduced cerebral volume. In the present study, cerebral volume was significantly reduced in patients with unfavorable outcome. As expected, RCV was also negatively correlated with age as well as with the extent of LA. However, a multivariate regression analysis identified cerebral atrophy as an independent predictor of unfavorable outcome after 3 months besides LA, the initial hematoma volume, and GCS score. Also, the RCV was significantly correlated with the outcome only in the youngest and oldest subgroups, which further stresses an independent effect of cerebral atrophy.

In large ischemic strokes in the middle cerebral artery territory, cerebral atrophy seems to counteract the evolution of malignant infarction, and thereby may favor survival. We calculated the ratio between the cerebral and the intracranial volume. This technique has been already established and has resulted in a very high inter-rater agreement in the present analysis.

In the study by Lee et al, cerebral atrophy not only reduced the odds for malignant outcome but also for acceptable functional outcome (mRS<4). Preexisting neurodegenerative processes seem to be a likely explanation for this association. In 2 studies, Tang et al, using the same volumetric approach as we did, have shown that cerebral atrophy in ischemic stroke patients is associated with prestroke as well as with poststroke dementia. According to that, all these parameters were significantly different between patients with favorable and unfavorable outcomes in the present study. Recently, ischemic LA could be identified as a novel risk factor for unfavorable outcome in ICH after being already recognized as a predictor of poor outcome in ischemic stroke. Using the same score to assess LA, we found it to be significantly more severe in patients with unfavorable outcome. Another risk factor for unfavorable outcome after ischemic stroke is reduced cerebral volume. In the present study, cerebral volume was significantly reduced in patients with unfavorable outcome. As expected, RCV was also negatively correlated with age as well as with the extent of LA. However, a multivariate regression analysis identified cerebral atrophy as an independent predictor of unfavorable outcome after 3 months besides LA, the initial hematoma volume, and GCS score. Also, the RCV was significantly correlated with the outcome only in the youngest and oldest subgroups, which further stresses an independent effect of cerebral atrophy.

Whereas studies in ischemic stroke used intercerebral measurements, which may overrate internal atrophy, we performed a semiautomatic threshold-based segmentation to assess cerebral volume more accurately. Furthermore, we calculated the ratio between the cerebral and the intracranial volume. This technique has been already established and has resulted in a very high inter-rater agreement in the present analysis.

Conclusions

We found cerebral atrophy to be an independent risk factor for unfavorable outcome after spontaneous supratentorial ICH. This indicates a reduced recovery potential in these individuals, which may be attributable to a preexisting neurodegenerative process.

Disclosures

None.

References

8. Fogelholm R, Nautila M, Vuorela AL. Primary intracerebral haemorrhage in the Jyväskylä region, central Finland, 1985-89: incidence, case...
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