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Hypertensive Intracerebral Hemorrhage in Young People
Previously Unnoticed Age-Related Clinical Differences

José L. Ruiz-Sandoval, MD; Samuel Romero-Vargas, MD; Erwin Chiquete, MD, PhD; Juan J. Padilla-Martínez, MD; Jorge Villarreal-Careaga, MD; Carlos Cantú, MD, MSc; Antonio Arauz, MD, MSc; Fernando Barinagarrementeria, MD

Background and Purpose—Hypertensive intracerebral hemorrhage (ICH) in young people has been the object of only succinct analyses. Therefore, it is unclear whether extrapolation of the information obtained from older patients is also valid for the young. Here we describe young persons with hypertensive ICH and compare them with their older counterparts to determine whether age-related clinical differences exist.

Methods—From 1988 to 2004, we studied 35 consecutive young patients with ICH (60% men; mean age, 33 years; range, 15 to 40 years) for whom the etiology of the brain hemorrhage was hypertension. For clinical comparisons, sex-matched persons with hypertensive ICH, aged >40 years, were randomly selected by a factor of 3:1 (n=105).

Results—Essential hypertension was present in 26 (74%) young patients and secondary hypertension in 9 (26%), with renovascular hypertension being the most common cause (n=5, 55%). Compared with older patients, the young had higher blood pressures, smaller hemorrhage volumes, lower rates of ventricular extensions (for all, P<0.05), and different distribution pattern of ICHs (P=0.05), without cerebellar and lobar locations. Thirty-day mortality was markedly lower in the young than in older persons (P=0.001), nevertheless at the expense of more incapacitating disabilities.

Conclusions—Young people presenting with hypertensive ICH differ in clinical characteristics and have a different prognosis when compared with their older counterparts. These findings suggest underlying age-related differences in disease pathogenesis. (Stroke. 2006;37:2946-2950.)

Key Words: aging ■ intracerebral hemorrhage ■ hypertension ■ risk factors ■ young people

Intracerebral hemorrhage (ICH) accounts for 10% to 23% of strokes, with hypertension being the single most important risk factor in middle-aged and elderly persons. Current knowledge about hypertensive ICH in the young is derived mainly from studies on all-cause ICH, which have reported variable frequencies ranging from 11% to 64% and providing only brief conclusions about topography and prognosis. The other well-characterized clinical and radiological characteristics of middle-aged and elderly ICH patients are generally unknown for their younger counterparts. Therefore, extrapolation of the information obtained from older people might not be valid for young persons.

In view of the scarce information on these issues, we aimed to analyze hypertensive ICH in young people, their hypertension profile, clinical condition, and outcome. Also, to identify features that would suggest underlying age-related differences in disease pathogenesis, we compared the young patients with their older counterparts. Our hypothesis was that hypertensive ICH of the young differs in clinical characteristics and has a different prognosis, when compared with that seen in older people.

Subjects and Methods

Study Population and Design

From January 1988 to December 2004, we analyzed 294 consecutive patients with symptomatic ICH who were <40 years old. From 1988 to 1998, the Instituto Nacional de Neurología y Neurocirugía (Mexico City, Distrito Federal, Mexico) included 244 patients, and from 1999 to 2004, the Hospital Civil de Guadalajara Fray Antonio Alcalde (Guadalajara, Jalisco, Mexico) included 50 patients in the respective research databases. Of the 294 young patients, hypertension was the cause of ICH in 35 (12%). To identify possible age-related clinical differences, sex-matched persons with hypertensive ICH, aged >40 years, were randomly selected by a factor of 3:1.
(n=105). The same inclusion criteria were applied for all patients. The internal Ethics Committee of our hospitals approved the study, and informed consent was obtained from all patients or their closest relatives.

Operational Definitions
In all cases included, ICH was defined as a sudden, focal, neurological deficit with intraparenchymal hemorrhage seen on head computed tomography (CT) scans. Hypertensive status was defined as a patient history of hypertension, with or without treatment, or average readings of systolic blood pressure (SBP) >140 mm Hg or of diastolic (DBP) >90 mm Hg, sustained for >2 weeks after the hospital admission and confirmed during follow-up, if suitable. Other potential causes of ICH were excluded. The BP readings obtained at presentation to the Emergency Department were considered for analyses to evaluate the discrete point of evolution of the ICH in which the first clinical evaluations and decisions were performed. Brain hemorrhage volume was calculated by analysis of CT scans according to the ABC/2 method. Obesity was defined as a body mass index ≥30 kg/m², smoking habit as the consumption of ≥5 cigarettes at least 2 days per week during 12 months or more, and alcoholism as >2 alcoholic drinks per day. Mean arterial pressure (MAP) was calculated from the BP measurement on admittance to the Emergency Department as follows: MAP=DBP+0.412 (SBP–DBP). Every young patient received an exhaustive clinical, radiological, and laboratory assessment for secondary hypertension. The Sokolow–Lyon criteria were used to define findings as suggestive of left ventricular hypertrophy on the ECG. The patient’s functional status was evaluated at hospital discharge and during follow-up by using the Glasgow Outcome Scale.

Data Analysis
Pearson $\chi^2$ and Fisher exact test were used to assess nominal variables in bivariate analyses. To compare quantitative variables distributed between the 2 groups, Student $t$ test and the Mann-Whitney $U$ test were performed for the distributions of parametric and nonparametric variables, respectively. Pearson correlation was used for continuous variables. All probability values were 2-sided and considered significant when $P<0.05$. The SPSS (SPSS Inc) v12.0 statistical package was used for all calculations and the process of randomization and selection of the comparison group.

Results
We studied 35 consecutive young patients with hypertensive ICH, 21 (60%) men and 14 (40%) women. Mean±SD age was 33±6.2 years (range, 15 to 40 years). One (3%) patient was <20 years, 11 (31%) were between 21 and 30 years, and 23 (66%) were between 31 and 40 years. In addition to the head CT scan, nine (26%) patients also underwent magnetic resonance imaging and 14 (40%) were investigated further with conventional cerebral angiography. Three (8.6%) patients had a history of prior ICH.

Hypertension Profile
Twenty-seven (77%) patients had known their hypertensive status at the time of ICH, and in 8 (23%) the diagnosis of hypertension was performed while hospitalized and confirmed during follow-up. In the 27 patients with antecedent hypertension, the mean time from the diagnosis to ICH was 43 months (range, 1 month to 20 years); in 4 (15%) patients, this period was <1 year; in 16 (59%), 1 to 5 years; and in 7 (26%), >5 years. Twenty (74%) patients had received pharmacological treatment, and of them, only 7 (35%) declared to be at least 80% compliant with their antihypertensive regimen. The ICH volume was higher in patients without treatment than in those with antihypertensive medication (Table 1).

By ECG records and chest films review, evidence of left ventricular hypertrophy was found in 28 (80%) patients. A secondary cause of hypertension was identified in 9 (26%) patients, renal artery stenosis being the cause in 5 (1 of them with Takayasu disease) and Cushing syndrome, aortic coarctation, primary aldosteronism, and pheochromocytoma in 1 case each.

<table>
<thead>
<tr>
<th>TABLE 1.</th>
<th>Clinical Characteristics and Outcome of the 35 Young Patients With Hypertensive ICH, According to Antihypertensive Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>Present (n=20)</td>
</tr>
<tr>
<td>Age, median (SD), y</td>
<td>33.3 (6.6)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>10 (50)</td>
</tr>
<tr>
<td>BP profile at hospital admission</td>
<td></td>
</tr>
<tr>
<td>SBP, mean (SD), mm Hg</td>
<td>197.55 (49.6)</td>
</tr>
<tr>
<td>DBP, mean (SD), mm Hg</td>
<td>125.20 (22.4)</td>
</tr>
<tr>
<td>MAP, mean (SD), mm Hg</td>
<td>155.01 (31.6)</td>
</tr>
<tr>
<td>ICH characteristics and outcome</td>
<td></td>
</tr>
<tr>
<td>ICH volume, mean (SD), cm³</td>
<td>8.8 (6.7)</td>
</tr>
<tr>
<td>Irruption to ventricles, n (%)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Disabilities, n (%)†</td>
<td>12 (60)</td>
</tr>
<tr>
<td>Disabilities or death</td>
<td>18 (90)</td>
</tr>
<tr>
<td>at 30 days, n (%)</td>
<td></td>
</tr>
<tr>
<td>30-day mortality, n (%)</td>
<td>6 (30)</td>
</tr>
</tbody>
</table>

$^*$P value for differences between patients with and without antihypertensive treatment; Pearson $\chi^2$, Fisher’s exact test, Student $t$ test, or Mann-Whitney $U$ test, as appropriate.
†A Glasgow Outcome Scale classification of II or III.

ICH Features and Outcome
The brain hematomas were located in the putamen in 18 (51%) patients, the thalamus in 9 (26%), the pons in 5 (14%), and the medulla, midbrain, and caudate nucleus in 1 (3%) case each. Extension into the ventricular system occurred in 10 (29%) patients, 6 of them with hemorrhage in the thalamus, 3 in the putamen, and 1 in the caudate nucleus. The mean time of hospitalization was 14 days (range, 0 to 43 days). Twenty-five (71%) patients received medical treatment for ICH and 10 (29%), a neurosurgical procedure (hematoma evacuation in 4 and ventriculostomy alone in 5; 1 patient received both procedures). In-hospital death occurred in 8 (23%) patients, 6 (17%) were discharged with total dependence on others for daily activities, and 16 (46%) were discharged with severe and 5 (14%) with mild disabilities. No patient was discharged with complete recovery. The patients who survived to discharge lived for at least 30 days; therefore, both in-hospital and 30-day mortality was the same. MAP was higher in patients who had died than in survivors at 30 days (170.8 versus 144.9 mm Hg, respectively; $P=0.047$). Twenty-six (96%) of the 27 survivors had at least 1 follow-up visit. The mean follow-up period was 18.7 months (range, 1 to 96 months). At the last follow-up visit, only 4 (15%) patients finally achieved total recovery, 13 (50%) remained with moderate dependence, and 6 (23%) remained
with total dependence on others for activities of daily living. Four (15.4%) of the 26 patients with suitable follow-up experienced rebleeding during this period, 1 of them with a history of prior ICH. Among the 3 patients without a history of ICH, the pattern of recurrence was ganglia-ganglia in 2 and brain stem–ganglia in 1. The patient with prior ICH presented with 2 rebleeding episodes during an 8-month outpatient follow-up, and all hematomas were located in the basal ganglia. This 39-year-old man had an abdominal pheochromocytoma and was discharged in a vegetative state after the last event.

Young Versus Older Patients
Compared with older patients, the young had a higher frequency of alcoholism and fewer cases of diabetes mellitus (Table 2). Notably, the BP readings were higher in the young than in older persons (Table 2); however, there were smaller volumes of the hematomas and fewer cases of ventricular involvement. Thirty-day mortality was markedly lower in young patients than in the older, nevertheless at the expense of a high number of cases with incapacitating disabilities (Table 2). Compared with older persons, the young had a different pattern of ICH location, with more brainstem hematomas and without the occurrence of lobar or cerebellar ICH (the Figure).

Discussion
Hypertensive ICH in young people is relatively uncommon when other putative causes are excluded by an exhaustive investigative protocol. We observed few cases before the third decade of life, which underscores the association of age with both hypertension and brain hemorrhage.

Hypertension Profile of the Young
The frequency of secondary hypertension in our young cohort was higher than that reported for hypertensive persons without ICH.21 Because the screening protocol for secondary hypertension is not systematically practiced in our centers for all persons, we could not determine the frequency of secondary hypertension in the older group. Nevertheless, secondary hypertension causing ICH might be more frequent in young people than it is in older persons, an issue that, however, needs more study. Moreover, despite the relatively short period between the diagnosis of hypertension and the occurrence of ICH in the young cohort, we found features of target-organ damage commonly attributed to chronic exposure to hypertension.22

Clinical and Radiological Age-Related Differences
At admission to the Emergency Department, the young had higher BP readings than the older patients. The reason for this aggravated BP profile in the young at hospital presentation might be due to either to hyperactivity of the autoregulation mechanisms of perfusion in response to brain damage or a distinct pattern of hypertension of the young (ie, secondary hypertension), compared with older patients. The young

### Table 2. Risk Factors, Clinical Characteristics, and Outcome of 35 Young Patients and 105 Sex-Matched Persons With Hypertensive ICH and >40 Years

<table>
<thead>
<tr>
<th>Variables</th>
<th>All Patients</th>
<th>Persons Aged ≤40 Years (n=35)</th>
<th>Persons Aged &gt;40 Years (n=105)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>57 (18–99)</td>
<td>35 (18–40)</td>
<td>65 (42–99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>84 (60)</td>
<td>21 (60)</td>
<td>63 (60)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity, n (%)</td>
<td>62 (44)</td>
<td>18 (51)</td>
<td>44 (42)</td>
<td>0.33</td>
</tr>
<tr>
<td>Alcoholism, n (%)</td>
<td>23 (16)</td>
<td>10 (29)</td>
<td>13 (12)</td>
<td>0.02</td>
</tr>
<tr>
<td>Smoking habit, n (%)</td>
<td>29 (21)</td>
<td>5 (14)</td>
<td>24 (23)</td>
<td>0.28</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>29 (21)</td>
<td>3 (9)</td>
<td>26 (25)</td>
<td>0.04</td>
</tr>
<tr>
<td>Previous ICH, n (%)</td>
<td>17 (12)</td>
<td>3 (9)</td>
<td>14 (13)</td>
<td>0.45</td>
</tr>
<tr>
<td>BP profile at hospital admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mean (SD), mm Hg</td>
<td>160.86 (68.1)</td>
<td>187 (45.3)</td>
<td>152.15 (72.3)</td>
<td>0.008</td>
</tr>
<tr>
<td>DBP, mean (SD), mm Hg</td>
<td>97.32 (41.1)</td>
<td>125.54 (28)</td>
<td>87.91 (40.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAP, mean (SD), mm Hg</td>
<td>123.50 (51.1)</td>
<td>150.86 (32.6)</td>
<td>114.38 (52.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICH characteristics and outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH volume, mean (SD), cm³</td>
<td>32.9 (32.4)</td>
<td>20.3 (15.3)</td>
<td>34.1 (33.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Irruption to ventricles, n (%)</td>
<td>74 (53)</td>
<td>10 (29)</td>
<td>64 (61)</td>
<td>0.001</td>
</tr>
<tr>
<td>Surgical treatment, n (%)†</td>
<td>67 (48)</td>
<td>10 (29)</td>
<td>57 (54)</td>
<td>0.008</td>
</tr>
<tr>
<td>Severe disabilities, n (%)‡</td>
<td>48 (34)</td>
<td>22 (81)</td>
<td>59 (56)</td>
<td>0.001</td>
</tr>
<tr>
<td>30-day mortality, n (%)</td>
<td>67 (48)</td>
<td>8 (23)</td>
<td>59 (56)</td>
<td>0.001</td>
</tr>
<tr>
<td>Severe disabilities or 30-day mortality, n (%)</td>
<td>115 (82)</td>
<td>30 (86)</td>
<td>85 (81)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

*P value for differences between patients aged ≤40 years and older patients; Pearson χ², Fisher’s exact test, Student t test, or Mann-Whitney U test, as appropriate.
†Hematoma evacuation, ventriculostomy, or both.
‡A Glasgow Outcome Scale classification of II or III.
cohort and their older counterparts differed in the location pattern of the brain hematomas. These differences in ICH location might be related to the effect of the aging process on the cerebral blood vessels.26–28 Thus, on one hand, more ICHs located in deep regions of the brain were observed in young persons, and on the other, more lobar hematomas were found in older people. Regarding this issue, the important role of cerebral amyloid angiopathy in hypertensive ICHs of lobar location has been demonstrated.27 However, the sample size included in the present report may be underpowered to detect some differences, and on the contrary, may exaggerate other small disparities between the young and older patients. Further studies are necessary to confirm our findings. Also, it remains to be defined whether the length of exposure to hypertension, the type of antihypertensive medication, and the management of associated risk factors can influence ICH location.

We could not find any correlation between hematoma size and BP readings, and despite having a higher MAP, the young had smaller hematomas and a lower rate of ventricular extensions than did the older patients. These findings suggest that the vascular disease and parenchymal degeneration observed with the aging process are important factors that may contribute to the more catastrophic effect of ICH in older people.29 Our observations are in agreement with recent evidence of the negative effect of aging on ICH-induced brain injury.30,31 We hypothesize that the aging process may imply changes in brain plasticity, diminishing the strength of the brain tissue that normally acts as a restriction wall to the extension of the hematoma. However, other factors can also affect the volume and extension of ICHs. It has been shown that some altered coagulation markers not routinely measured in clinical practice are associated with the rapid expansion of hypertensive hemorrhages.32

In summary, hypertensive ICH in the young differs in several features from that of older patients, which in turn suggests underlying distinctions in disease pathogenesis. Our findings warrant further investigation on the influence of the aging process in hypertensive ICH.

Disclosures

None.

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