Age-Related Spontaneous Intracerebral Hematoma in a German Community

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We investigated incidence, age distribution in relation to etiology, and localization of spontaneous intracerebral hematoma in 100 consecutive cases. Incidence in the total population of the Giessen area was estimated to be >11/100,000 inhabitants/yr and increased with age. There was a trend toward higher incidence in males. Overall mortality was 27%, 22% of 58 patients aged <70 years and 33% of 42 patients aged ≥70 years. Hypertensive putaminal hematoma showed the highest mortality rate (42%, 10 of 24 cases). Chronic alcoholism and anticoagulant medication influenced the mortality rate unfavorably. We found the following localizations and etiologies to have a specific relation with age: 1) lobar hematomas from vascular malformations, group aged <40 years; 2) hypertensive putaminal hematomas and hypertensive thalamic hematomas, group aged 40–69 years; and 3) lobar hematomas, group aged ≥70 years. Alcoholism was an additional factor in 38% of the 13 middle-aged men with hypertensive putaminal hematomas. Fourteen cases of spontaneous intracerebral hematoma were possibly due to cerebral amyloid angiopathy. Six of these 14 patients had recurrent lobar hematomas, but only three of the six could be histologically investigated. In these three cases, cerebral amyloid angiopathy was proven. (Stroke 1990;21:1412-1418)

Spontaneous hemorrhage is a phenomenon particular to the brain and associated structures, not occurring in other organs. A number of different changes in the cerebral vasculature can lead to spontaneous intracerebral hematomas. The type of vascular changes determines the localization and clinical course of the hemorrhage. Vascular factors have a distinct relation with age at the time of hemorrhage. The most common cause of nontraumatic intracerebral hematoma in young adults is the rupture of vascular malformations. Spontaneous intracerebral hematoma in middle-aged adults is most commonly attributable to hypertensive vascular disease. In recent years it has been recognized that cerebral amyloid angiopathy is an important cause of spontaneous intracerebral hematoma in the elderly; therefore, hematomas in the elderly to a certain extent have a different course. In contrast to other European countries, little is known about the occurrence of spontaneous intracerebral hematomas in the population of the Federal Republic of Germany. Therefore, we determined the incidence of this disease in a West German community. Furthermore, we investigated the question of the relation of hematomas with age and sex in this patient collective.

Subjects and Methods

We studied all 100 patients with spontaneous intracerebral hematomas admitted to the neurological department of the University Hospital of Giessen during 33 months starting in July 1985. The diagnosis of spontaneous intracerebral hematoma was established with axial computed tomography in all cases. In 1987, the area of Giessen had a population of 235,000. However, because a number of patients with intracerebral hematomas were admitted to the local neurosurgical department and because some elderly patients were treated in local general hospitals, not all patients who suffered this disease during this period were included. A certain number of patients from outside the local population were admitted. The age-related incidence of spontaneous intracerebral hematoma in the Giessen area was calculated for 1987. In a second step, the age and sex distribution of the entire patient collective was computed on the basis of the Giessen area population structure in 1987.

Hypertensive spontaneous intracerebral hematoma was diagnosed if the patient had a definite history of hypertension or a systolic blood pressure of >150 mm Hg and a diastolic blood pressure of >90
mm Hg. Patients without a history of hypertension were also diagnosed as having hypertensive spontaneous intracerebral hematoma if their blood pressure was hypertensive on admission and signs of cardiac hypertrophy were seen on roentgenography or electrocardiography. Spontaneous intracerebral hematoma of unknown etiology was diagnosed if either hypertensive blood pressure was not observed or if a transient elevation of systolic blood pressure in a patient with a large space-occupying hematoma or a pontine hematoma could be attributed to autonomic dysregulation. In such cases, electrocardiograms and chest x-ray films did not show left ventricular hypertrophy and blood pressure normalized after the acute phase. The volumes of 52 hypertensive hematomas and 21 hematomas of unknown etiology were measured planimetrically. The odds ratio for hypertension was computed by comparing the incidence of hypertension in patients with spontaneous intracerebral hematoma aged 20–69 years with the incidence of hypertension in the 2,409 men and 2,370 women aged 20–69 years of the nationwide German DHP Study.6

Hematomas were localized according to the classification of Fisher7 as putaminal, lobar, thalamic, cerebellar, or pontine. To this we added hematomas of the candate nucleus. Very large hematomas including the entire basal ganglia and not identifiable as arising from the putamen or thalamus were classified as total basal ganglia hematomas.8,9

The $\chi^2$ test and, if appropriate, Fisher’s exact test were used for statistical evaluation.

**Results**

Age in the 100 patients varied from 21 to 93 years; the median age was 66 years, with peak incidence of spontaneous intracerebral hematoma in patients aged 70–79 years (Figure 1). Sex distribution was 60% men and 40% women (Table 1), with peak incidence of spontaneous intracerebral hematoma in men aged 60–69 years and in women aged 70–79 years. The patients were also classified into three age groups, with six patients in the group aged <40, 52 in the group aged 40–69, and 42 in the group aged ≥70 years.

Twenty-seven patients admitted during 1987 came from the Giessen area; incidence for 1987 was correspondingly calculated to be 11.48/100,000 (95% confidence interval (CI) 7.86–16.657) inhabitants. The effective incidence is somewhat higher because elderly stroke patients treated in general hospitals and some neurosurgically treated patients were not included. The age and sex distribution of the entire patient collective compared with the age and sex distribution of the Giessen area in 1987 (Table 2) shows a strongly increasing incidence of spontaneous intracerebral hematoma with age. Though there was a general tendency toward increased incidence in men, especially those aged 40–49 years (partly due to alcoholism), a clear difference between the sexes could not be found since the 95% CIs overlapped considerably (Table 2).

**Table 1. Age and Sex Distribution of Patient Collective With Spontaneous Intracerebral Hematoma Over 33 Months**

<table>
<thead>
<tr>
<th>Sex</th>
<th>20–29</th>
<th>30–39</th>
<th>40–49</th>
<th>50–59</th>
<th>60–69</th>
<th>≥70</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>9</td>
<td>23</td>
<td>40</td>
</tr>
<tr>
<td>Men</td>
<td>2</td>
<td>2</td>
<td>14</td>
<td>8</td>
<td>15</td>
<td>19</td>
<td>60</td>
</tr>
</tbody>
</table>

Data are number of patients.
Hypertension proved to be a powerful risk factor for spontaneous intracerebral hematoma since the odds ratio was 16.335 (95% CI 13.17–18.233) for men and 45.19 (95% CI 23.5–86.9) for women. Fifty-nine patients had hypertension (Figure 2); six of these 59 were also receiving warfarin treatment. Twenty-five patients had spontaneous intracerebral hematomas of unknown etiology; in three of these 25 patients cerebral amyloid angiopathy could be proven histologically (see below). In six patients treatment with warfarin was the only risk factor for cerebrovascular disease. Hemorrhage from vascular malformations was seen in six patients. Two patients had neoplastic hemorrhage, in one patient hemorrhage was due to rupture of an aneurysm of the circle of Willis, and in the remaining patient the intracerebral hematoma was due to a hemorrhagic diathesis.

Nine patients, all men, had spontaneous intracerebral hematomas and chronic alcoholism. In seven patients alcoholism was associated with hypertension, and three of these seven had hepatic cirrhosis; one alcoholic patient had a ruptured angioma. In one patient no risk factor for cerebrovascular disease other than alcoholism was found. Thrombocytopenia (<60,000 platelets/mm²) was not seen in any alcoholic patient. Their average age was only 47 years; all but one were 40–69 years old. Five alcoholic patients belonged to the subgroup of 13 men with hypertensive putaminal hemorrhage in the group aged 40–69 years (see below). Three alcoholic patients died, including one with liver cirrhosis.

Etiology of spontaneous intracerebral hematoma was related to age (Figure 3). Of the six patients aged <40 years, four (67%) had vascular malformations (including two with so-called small vascular malformations), only one patient (17%) had hypertension, and the other had a hemorrhagic diathesis. Of the 52 patients aged 40–69 years, 38 (73%) had hypertension (including six with alcoholism), six (12%) had hematomas of unknown etiology, four (8%) had hemorrhage under treatment with warfarin, two (4%) had vascular malformations, one bled due to neoplasm, and the other bled due to rupture of an aneurysm. Of the 42 patients aged ≥70 years, 20 (48%) had hypertension, 19 (45%) had hematomas of unknown etiology, two had hemorrhage under treatment with warfarin, and one had a hemorrhagic neoplasm. Patients with hypertensive hematomas...

Etiology

% 80 60 40 20 0

Age (n) > 69 (42) 40–69 (52) < 40 (6)

FIGURE 3. Histogram of age-related etiology of spontaneous intracerebral hemorrhage in 100 consecutive patients. Hematomas in patients aged <40 years were caused by ruptured vascular malformations in four of six cases. Among patients aged 40–69 years, 73% had hypertension including six who were alcoholic. Among patients aged >69 years, 48% had hypertension and 45% had hematomas of unknown etiology. Hyper., hypertension; Unkn., unknown; Warf., treatment with warfarin; SAH, subarachnoid hemorrhage (ruptured aneurysm of circle of Willis); V. malf., vascular malformation; H. diat., hemorrhagic diathesis.

were significantly younger (mean age 63 years) than those with hematomas of unknown etiology (mean age 76 years) (p<0.05).

Putaminal hematomas were the most common (31 cases, Figure 2). Lobar hematomas followed with 27 and thalamic hematomas with 26 cases; seven patients had cerebellar hematomas, and three had pontine hematomas. Three patients had hemorrhaged into the head of the caudate nucleus, and three had total basal ganglia hematomas. Localization was age-related. The group aged <40 years more commonly had lobar hematomas (50%); only one patient had a putaminal hematoma, one had a cerebellar hematoma, and one had hemorrhaged into the head of the caudate nucleus. In the group aged 40–69 years, 19 (37%) had putaminal hematomas, 18 (35%) had thalamic hematomas, five (10%) had lobar hematomas, three (6%) had cerebellar hematomas, and three (6%) had pontine hematomas; two patients (4%) had hemorrhaged into the head of the caudate nucleus, and the other two (4%) had total basal ganglia hematomas. Of the group aged ≥70 years, only 11 (26%) had putaminal hematomas, 19 (45%) had lobar hematomas, eight (19%) had thalamic hematomas, three (7%) had cerebellar hematomas, and one (2%) had a total basal ganglia hematoma.

Comparing localization and etiology in all 100 patients (Figure 2) allows identification of three prominent types of spontaneous intracerebral hematoma: 1) hypertensive putaminal hematoma (24 of 100 patients), 2) hypertensive thalamic hematoma (21 of 100 patients), and 3) lobar hematoma of unknown etiology (14 of 100 patients). Analysis of the three age groups shows age-specificity of the three prominent types. In the group aged <40 years, lobar hematoma (due to rupture of vascular malformations in two and to hemorrhagic diathesis in the other) predominated (50%). In the group aged 40–69 years, hypertensive hematoma was most common (73% [38] of the 52 hematomas in the group, 38% of all 100 hematomas). Further anatomic differentiation shows that in this group hypertensive putaminal hematoma and hypertensive thalamic hematoma were equally represented, each with 31% (16) of the 52 hematomas. Alcoholism was an additional risk factor for men; five (38%) of the 13 men in this age group with hypertensive putaminal hematoma were alcoholics. In the group aged ≥70 years, lobar hematoma of unknown etiology occurred in 33% (14 of the 42 cases), followed by lobar hematoma of hypertensive etiology in 17% (seven of the 42 cases).

Eight of the 100 patients had suffered a first hemorrhage 6 months to 6 years earlier. One patient with severe hypertension first suffered a left and then a right thalamic hematoma 4 years later. A second patient had severe hypertension associated with recurrent contralateral putaminal hematoma. The remaining six patients, all aged ≥70 years, suffered lobar hematomas of unknown etiology and thus were suspected of having cerebral amyloid angiopathy. Two of these six patients died, and in a third the hematoma was treated by surgery; in all three cases cerebral amyloid angiopathy was diagnosed histologically.

Twenty-seven patients died, none in the group aged <40 years. In the group aged 40–69 years, 13 (25%) died. In the group aged ≥70 years, 14 (33%) died (p=0.3). In the two latter age groups 70% of the
The localization of the 100 hematomas in our study is comparable to that in a study of 100 unselected patients conducted by Kase and Mohr.3 We found hypertension to be a powerful risk factor for spontaneous intracerebral hematomas but less important than in older studies due to the decrease in the importance of hypertension as a risk factor for cerebrovascular disease,10-12 to our recognition of alternative etiologies such as cerebral amyloid angiopathy, and to our diagnosis of intracerebral hematoma by computed tomography compared with autopsy.13,14 The percentage of our patients receiving anticoagulant medication was higher (12%) than in a contemporary study.15 However, half of our patients receiving warfarin also had hypertension. Compared with the pathoanatomic study of Boudouresques et al16 in which 16.5% of hematomas were attributed to alcoholism, this condition was less frequent (9%) in our investigation. Furthermore, seven of the nine alcoholic patients were also hypertensive, and only three had hepatic cirrhosis.

The incidence of spontaneous intracerebral hematomas could not be defined precisely by our study because a number of elderly patients were treated in general hospitals and because some surgically treated patients were not included. The incidence was somewhat higher than 11/100,000/yr, probably comparable to that in the Caucasian population of North America.10,17 Our study confirmed the increasing incidence of spontaneous intracerebral hematoma with age in the elderly.10 Every second patient was ≥66 years old. Peak morbidity occurred in those aged 70-79 years (Figure 1). There was a trend toward male predominance (Table 2), with incidence in all age groups 1.6-2.6 times higher in men than in women. This result was comparable to that in the Hisayama Community Study,18 in which there was a male predominance in patients aged >70 years.

In our small group of six patients aged <40 years, four hematomas (67%) were due to ruptured vascular malformations, which is also reported to be the most common cause of spontaneous intracerebral hematomas in young adults in other studies19,20 (from 29% to 57%2,21). From 57% to 70% of such hematomas are lobar hematomas,2,21 due to the preferential localization of vascular malformations in the central and parietal regions as well as in the temporal and frontal lobes.22 Hemorrhages into the head of the caudate nucleus are suspected of being due to rupture of a small vascular malformation if risk factors for cerebrovascular disease are lacking. Such hematomas can also mimic primary ventricular hemorrhage or subarachnoid hemorrhage without identifiable aneurysm.23,24 Rarely, rupture of an aneurysm in the internal carotid artery causes a hematoma in the head of the caudate nucleus.25 Hematomas due to small vascular malformations in the cerebellum, as in one patient (Figure 2), constitute up to 28% of all cryptic vascular malformations.26 The frequency of hypertensive hematomas in our group aged <40 years (one case, 17%) was comparable to the 15% found by Toffol et al.2

Spontaneous intracerebral hematomas in our group aged 40-69 years were most often caused by hypertensive vascular disease (Figure 3). Alcoholism and treatment with warfarin were additional risk factors (six cases each). As hypertensive vascular changes (lipohyalinosis, microaneurysm, fibrinoid necrosis)26-28 are most prominent in the thalamus and basal ganglia, hypertensive putaminal and hypertensive thalamic hematomas dominated in this age group. A remarkable result of our investigation is that more than a third of the hypertensive putaminal hematomas in men (five of 13 cases) were associated with chronic alcoholism. The high mortality rate for hypertensive putaminal hematomas is also remarkable (six of 16 [38%] in this age group, 12 [39%] of all 31 putaminal hematomas). A lethal outcome was facilitated in two cases by alcoholism and in two cases by warfarin treatment.15,30,31 In this age group mortality rates for hypertensive thalamic hematomas, all hypertensive hematomas, and all hematomas were 25% (four of 16), 29% (11 of 38), and 25% (13 of 52), respectively, confirming the worldwide trend to a more favorable prognosis.12,32,33 In this age group,
only six patients had spontaneous intracerebral hematoma of unknown etiology (Figure 3). Localization for such hematomas was comparable to that for hypertensive hematomas. It cannot be excluded that these patients did in fact have beginning hypertension and early hypertensive vascular disease with comparatively thin arterial walls.

In our study, patients aged ≥70 years were heavily represented (42% of the 100 cases). Comparison with the Cincinnati Community Study shows that this overrepresentation is not due to regional demographics. Conflicting statistics are reported by the Hisayama Community Study between 1974 and 1983, in which only 18% of patients with spontaneous intracerebral hematomas were ≥70 years old. Similar to a Swiss study, 23% of all our patients were women aged ≥70 years (Table 1), corresponding to the higher life expectancy of females in our population (see also Table 2). Mortality in this age group was surprisingly low (33%). Though hematoma volume in general did not depend on etiology, 10 (50%) of the 20 patients aged ≥70 years with hypertensive hematomas died, and 10 (71%) of the 14 fatal cases had hypertensive hematomas. Of the seven hypertensive putaminal hematomas, four (57%) were fatal. The comparatively low total mortality rate in this age group is attributable to the favorable prognosis of the many lobar hematomas of unknown etiology; only two of 14 patients with such hematomas died.

In contrast to earlier studies, in which only 16% and 46% lobar hematomas occurred in the older age groups, in our patient collective 70% (19) of the 27 patients with lobar hematomas were aged ≥70 years. Lobar hematomas of unknown etiology are even characteristic of the oldest age group, comprising 14% of the entire patient collective and 33% of the hematomas in patients aged ≥70 years. Discussion of the pathogenesis of this type of hematoma is decades old. For many years, cryptic vascular malformations have been suspected as a cause. We consider it difficult to explain why microangiomas should so often rupture in old age after being asymptomatic for more than 70 years. Therefore, to us the theory that these hematomas are caused by the rupture of miiliary microaneurysms appears more conclusive. Such miiliary microaneurysms are common in the subcortical white matter of the retrolorandic region and occur in hypertensive as well as normotensive elderly individuals. A more important mechanism of lobar hematomas in this age group is cerebral amyloid angiopathy.

A difficultly experienced by most investigators studying the incidence of amyloid angiopathy–related hematomas is the fact that such hematomas often carry a favorable prognosis and are seldom treated by craniotomy, so that suspicious cases often lack histologic confirmation. This may be why other studies show a low incidence of hematomas due to proven cerebral amyloid angiopathy, as did our study (only three cases histologically proven among 14 cases suspected). Hemorrhages due to cerebral amyloid angiopathy are also rare in pathoanatomic studies. Mollien and Schmitt found only five intracerebral hemorrhages due to congophilic angiopathy among 16,000 unselected autopsy cases. Jellinger found only 15 hematomas among 1,400 autopsy cases. Masuda et al. found only one case of cerebral amyloid angiopathy among 26 spontaneous intracerebral hemmorhages in elderly patients. Definition of the incidence of hemmorhages due to cerebral amyloid angiopathy is also complicated by concomitant hypertension in approximately 40% of patients. Ishii et al. diagnosed cerebral amyloid angiopathy in seven (12%) of 60 geriatric patients with cerebral hemorrhages. Vinters estimated that 5–10% of all spontaneous intracerebral hematomas are due to cerebral amyloid angiopathy. These frequencies correspond well to our 3% histologically proven, 6% highly probable, and altogether 14% suspicious cases of cerebral amyloid angiopathy.

References


KEY WORDS • cerebral hemorrhage • hematoma • incidence • Germany
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