Intracerebral Hemorrhage in Young People
Analysis of Risk Factors, Location, Causes, and Prognosis

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Background and Purpose—The frequency of intracerebral hemorrhages (ICHs) in people aged ≤40 years has been poorly studied. We investigated the incidence, causes, locations, and prognosis of ICH in young patients.

Methods—We evaluated all consecutive patients with neuroimaging evidence or pathological confirmation of symptomatic ICH. We excluded patients with primary subarachnoid or traumatic hemorrhage, past evidence of vascular malformation, or brain tumor. We analyzed the risk factors, number, locations, and causes of ICH, and final outcome measured by the modified Glasgow Outcome Scale.

Results—We retrospectively evaluated 200 patients (mean age, 27 years; range, 15 to 40 years). The most frequent risk factors were tobacco use (20%), hypercholesterolemia (35%), hypertension (13%), and alcohol use (10%). The locations of ICH were lobar (55%), basal ganglia/internal capsule (22%), and others (24%). The most common causes of ICH were vascular malformations (49%), including cavernous angioma, and hypertension (11%). Cryptogenic ICH was considered in 15%. Other causes included cerebral venous thrombosis (5%) and sympathomimetic drug use (4%). The majority of patients with ICH that resulted from hypertension were aged >31 years (odds ratio, 3.48), and those with ICH that resulted from arteriovenous malformations were aged <20 years (odds ratio, 2.80). The final outcome was considered favorable in 60%.

Conclusions—ICHs in young people are mainly lobar in location and result from vascular malformation. Hypertension causes most cases in which the ICH is located in the basal ganglia. Mortality and morbidity in the acute phase are low and are related to hypertension as the cause of ICH. (Stroke. 1999;30:537-541.)

Key Words: cerebral hemorrhage ■ prognosis ■ risk factors ■ young people

Spontaneous intracerebral hemorrhages (ICHs) account for approximately 10% of all stroke cases.1 The incidence of ICH in people aged <35 years has been estimated to be 0.3/100 000.2–3

The frequency of ICH among a series of stroke in young adults varies from 0.7% to 40%.4–5 The etiologic spectrum of ICH in young people may be wider than in older individuals and includes vascular malformations,6 hypertension,7 and drug use.8 Few series of ICH in young people have been published,6,7,9–15 and most do not provide a detailed discussion of the primary causes of ICH.

The goal of the present study was to describe the frequency of ICH and to provide a descriptive analysis of causes, location, and prognosis of ICH in an extensive and well-studied series of patients aged <40 years.

Subjects and Methods

Among 1734 consecutive patients admitted to our stroke clinic at National Institute of Neurology and Neurosurgery (urban tertiary medical center) from January 1986 to July 1997, 632 patients (36.4%) were aged <40 years; of these, 224 (35.4%) had a diagnosis of ICH, and 200 (31.6%) were considered eligible for final analysis. We retrospectively analyzed the clinical and radiological data from those patients with neuroimaging or neuropathological evidence of ICH.

The inclusion criteria were age ≤40 years at the time of ICH and availability of detailed clinical information relating to risk factors, clinical features, hospital course, and final outcome (clinical evaluation according to the Glasgow Outcome Scale at the time of the last visit). A good outcome was defined as a Glasgow Outcome Scale score of I or II; a poor outcome was defined as a Glasgow Outcome Scale score of III to V and documentation of ICH by CT or MRI.

We excluded those patients with primary subarachnoid and traumatic hemorrhages and those with a previously diagnosed vascular malformation, aneurysm, or brain tumor.

In each patient and control subject, we analyzed the risk factors, which were defined as follows: arterial hypertension, diastolic values >90 mm Hg and/or systolic pressure >160 mm Hg for >2 determinations, use of antihypertensive drugs, previous medical diagnosis of arterial hypertension, or any combination of these; diabetes mellitus, fasting glucose value >120 mg/dL at the time of admission; hypercholesterolemia, fasting cholesterol level >250 mg/dL at the time of admission; hypercholesterolemia, fasting cholesterol level <160 mg/dL at the time of admission; hypertriglyceridemia, fasting triglyceride level >150 mg/dL at the time of admission; rheumatic valve disease, history of rheumatic fever and cardiac evaluation compatible with cardiac valve disease (stenosis and/or mitral insufficiency and aortic valve lesions) with or without cardiac rhythm disturbance; tobacco use, daily use of ≥10 cigarettes during the
previous 6 months; alcohol use, ingestion of ≥100 g/d of alcohol during the previous 2 months or acute alcoholic intoxication during the 24 hours before the cerebral infarction; migraine, defined according to the International Classification Committee of the International Headache Society; and oral contraceptive use, regular use during the last 6 months.

Classification of each hematoma location was based on the location of the epicenter of the hematoma as lobar (frontal, parietal, temporal, occipital), thalamic, basal ganglia/internal capsule, cerebellar, or brain stem.

The etiology of ICH was defined in accordance with the following criteria: hypertension; ICH located in the putamen, thalamus, internal capsule, and brain stem, cerebellum, or white matter (including lobar); and documentation of hypertension by blood pressure readings >160/95 mm Hg (on ≥3 different readings) or actual treatment, as well as exclusion of other potential cause of ICH; arteriovenous malformation confirmed by MRI or cerebral angiography; cavernous angioma based on MRI criteria,16 ie, appearance of a reticulated core of mixed signal intensity with a surrounding rim of decreased signal intensity or neuropathological confirmation; venous angioma, ICH in topographical relation to venous angioma and exclusion of other potential causes; drug use, ICH in close temporal relation to ingestion of drugs and exclusion of other potential causes; hematologic disorders, ICH related to thrombocytopenia, leukemia, hemophilia, von Willebrand disease, a fibrinogenemia, and exclusion of other potential causes; tumor, ICH related to a previously silent brain tumor diagnosed by neuroimaging or neuropathological studies; anticoagulant use, ICH related to use of anticoagulants with overdose effect or less commonly as idiosyncratic response17; toxemia, ICH during pregnancy or the puerperium that appears in clinical context of hypertension, proteinuria, leg edema, seizures, and polyhydramnios; ICH during pregnancy or the puerperium that appears in clinical context of hypertension, proteinuria, leg edema, seizures, and polyhydramnios; ICH related to thrombocytopenia, leukemia, hemophilia, von Willebrand disease, a fibrinogenemia, and exclusion of other potential causes; tumor, ICH related to a previously silent brain tumor diagnosed by neuroimaging or neuropathological studies; anticoagulant use, ICH related to use of anticoagulants with overdose effect or less commonly as idiosyncratic response;17 toxemia, ICH during pregnancy or the puerperium that appears in clinical context of hypertension, proteinuria, leg edema, seizures, and consciousness disorder as well as exclusion of other potential causes;18 migraine, history of migraine, and prolonged migraine attack at onset of ICH and exclusion of other potential causes;19 cerebral venous thrombosis, ICH accompanying direct or indirect CT findings and confirmation of cerebral venous thrombosis through MRI or cerebral angiography;20 undetermined, patients with ICH in whom pertinent neuroimaging studies were not performed (this group included deceased patients in whom necropsy was not performed); and cryptogenic, patients without risk factors or predisposing conditions in whom structural abnormalities were not found on MRI or cerebral angiography to explain ICH and with follow-up during ≥6 months and with control neuroimaging studies.

For statistical analysis, the differences between groups were tabulated and analyzed with the use of the STATA program. The univariate analysis (odds ratio [OR] with 95% CI) was conducted with 2x2 contingency tables with statistical validation by x² or Fisher’s exact 2-tailed test for categorical variables. The results were considered statistically significant if the probability of occurrence was <0.05.

**Results**

We studied 200 patients (107 men [53%], 93 women [47%]; mean age, 27±6.7 years [range, 15 to 40 years]).

The most common risk factors included tobacco use in 20%, hypocholesterolemia in 35% (serum cholesterol level ≤160 mg/dL), hypertension in 13%, and alcohol use in 10%. The frequency of risk factors based on age is shown in Table 1. Multivariate analysis indicated that hypertension was more common in patients aged ≥31 years (P=0.01). Hypcholes terolemia was more common in patients aged <20 years (OR, 4.87; 95% CI, 2.0 to 12.3) and in those with cryptogenic ICH (OR, 6.33; 95% CI, 2.14 to 20.8) and secondary to rupture of a vascular malformation (OR, 6.6; 95% CI, 3.91 to 14.8).

The most common locations of ICHs were lobar in 110 patients (55%), basal ganglia/internal capsule in 43 (22%), the brain stem in 26 (13%), cerebellum in 10 (5%), intraventricular in 8 (4%), and multiple in 3 (1.5%).

The most common causes of ICH were rupture of an arteriovenous malformation in 67 patients (33%), cavernous angioma in 32 (16%), and hypertension in 22 (11%). In 29 patients (15%) we could not demonstrate the cause of ICH, and in 12 patients (6%) the diagnostic workup was incomplete. Table 2 shows the relation between the location and the cause of ICH.

**Arteriovenous Malformations**

Among 67 patients with ICH and arteriovenous malformation, 45 (67%) were lobar in location (frontal in 13, temporal in 13, parietal in 10, occipital in 9). The posterior fossa was involved in 9 patients (13%). In 20 of 43 patients (47%) aged <20 years, the etiology of ICH was rupture of the arteriovenous malformation (P=0.03). In 45 of 110 patients (41%) with lobar ICH, the cause was arteriovenous malformation (P=0.02).

**Cavernous Angioma**

In 13 of 36 patients (36%) with an ICH located in the posterior fossa, the cause was attributed to cavernous angioma (P=0.0002). Among 32 patients with cavernous angioma, 19 (59%) were located supratentorially and 13 (41%) infratentorially. Half of those patients with supratentorial cavernous angioma had a poor outcome compared with one third of those with angioma located infratentorially (P=0.03).

**Hypertension**

Twenty-two patients (11%) had an ICH that resulted from hypertension; 17 (72%) were aged ≥31 years (P=0.02), and in 16 the ICH was located in the basal ganglia (P=0.00). Among 16 survivors (73%), 4 (25%) had a recurrence during follow-up.

**Cryptogenic**

In 29 patients (15%), we could not determine the cause of ICH despite an extensive workup, including MRI. In almost half of the patients, ICHs were located in the lobar region.

**Cerebral Venous Thrombosis**

Ten patients (5%) had an ICH that resulted from cerebral venous thrombosis; in 9 the location of the ICH was lobar (P=0.02).

**Sympathomimetic Drugs**

The use of phenylpropanolamine was responsible for 7 cases (4%) of ICH. There was a positive association with the basal ganglia location (P=0.03).
Toxemia of Pregnancy

Toxemia of pregnancy caused ICH in 7 patients (4%). The most common location in these patients was ganglionic (P = 0.01).

The final outcome measured during the last visit was considered good (Glasgow Outcome Scale scores of I and II) in 119 patients (60%). Regarding prognosis, 9 patients (90%) with cerebral venous thrombosis had a good outcome, and 15 of 22 patients (68%) with hypertension had the worst prognosis (Table 3).

There were 25 deaths (8%) in the acute stage of ICH, and 17 surviving patients were lost during the follow-up period. During a mean follow-up of 17 months, there were 14 recurrences (9%). The frequency of recurrence in relation to the cause of ICH is shown in Table 4.

Discussion

ICH in young people is not well described in the literature. Several published series include patients aged >40 years,7,10 which increases the probability of hypertension as the main cause of ICH, such as occurred in the series of Fuh et al,7 in which 54% of patients with ICH related to hypertension were aged >40 years. For this reason, we chose an upper age limit of 40 years.

There was a low prevalence of risk factors related to age in this series, which was similar to those reported in other series of ischemic stroke in young people.21 Two of the most common risk factors included hypocholesterolemia and hypertension. Recent attention has focused on the association of hypocholesterolemia and an increased incidence of ICH.22,23 The mechanism underlying this relationship is unclear; however, an etiologic link has been suggested by the recent confirmation of this relationship in other Asian populations, Hawaiian individuals of Japanese ancestry, and white American men.24,25 The association of low cholesterol levels is not restricted to Asians.26 Some investigators have proposed that the interaction of high diastolic blood pressure and low cholesterol levels weakens the endothelium of the intracerebral arteries, resulting in hemorrhagic stroke in the presence of hypertension.26 In 35% (59 of 167) of our patients in whom cholesterol was measured, there were evidence of low cholesterol levels. This finding was significantly common in

<table>
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<th>TABLE 2. Frequency of Location of Intracerebral Hemorrhage by Cause</th>
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<td>AVM (n=67)</td>
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<tr>
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<td>Hypertension (n=22)</td>
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<td>Cryptogenic (n=29)</td>
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<tr>
<td>Undetermined (n=12)</td>
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<tr>
<td>CVT (n=10)</td>
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<tr>
<td>Drug use (n=7)</td>
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<td>Toxemia (n=7)</td>
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<td>Other (n=14)</td>
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AVM indicates arteriovenous malformation; CVT, cerebral venous thrombosis.

*P = 0.02 (lobar vs nonlobar).
†P = 0.000 (ganglionic vs nonganglionic).
‡P = 0.02 (lobar vs nonlobar).
§P = 0.03 (ganglionic vs nonganglionic).
¶P = 0.01 (ganglionic vs nonganglionic).

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<th>TABLE 3. Frequency of Neurological Sequelae and Death by Cause of ICH</th>
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GOS indicates Glasgow Outcome Scale; AVM, arteriovenous malformation; and CVT, cerebral venous thrombosis.

*P = 0.02 (GOS I and II vs III–IV).
†P = 0.00 (GOS V vs GOS<5).
‡P = 0.00 (GOS V vs GOS<5).

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<td>Brain tumor (n=4)</td>
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<tr>
<td>Others (n=35)</td>
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<td>Total</td>
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AVM indicates arteriovenous malformation.

*P = 0.001.
patients aged <20 years, in whom hypertension is uncommon (Table 1). Recently, Iribarren et al.27 described the association between low serum cholesterol level and cerebral hemorrhage confined to elderly men. Low cholesterol level has been related to acute medical events such as myocardial infarction.28 Woo et al.29 studied lipid values in patients with acute stroke and did not find changes in patients with ICH. The role of hypcholesterolemia as a cause of ICH should be investigated in future studies.

Hypertension was responsible for a low percentage of ICH in the present series (11%), however, and compared with other causes, this produced the worst outcome and resulted in high morbidity, mortality, and recurrence. Hypertension as a cause of ICH was most common in individuals aged >31 years. As traditionally reported, the ICH was often located in the basal ganglia. Interestingly, 45% of these patients were unaware of the presence of hypertension, and in those in whom hypertension had been previously diagnosed, treatment was irregular. Recurrence was documented in 30% of surviving patients with hypertension. The frequency of recurrence of cerebral hemorrhage, mainly in those cases related to hypertension, has been considered very low; however, recent and relevant information demonstrated that rebleeding after a first primary ICH is not uncommon and occurs in an average 3.8% of cases.30–33 The high frequency of recurrence in the present series could be partially explained by the fact that most patients could not achieve good blood pressure control. The mean blood pressure at hospital admission was 130 mm Hg. Increase in blood pressure is common in acute central nervous system lesions, but in these cases the natural history is favorable, with normalization after 24 hours in the majority of patients.34 All patients from our series with ICH related to hypertension had persistent increase of blood pressure.

The most common cause of ICH was rupture of vascular malformations, including both arteriovenous malformation and cavernous angioma. This finding is similar to that of previously reported series.6,7,10,14,15 The most common location of ICH resulting from arteriovenous malformations was lobar. Cavernous angioma was most commonly located supratentorially but was the most common cause of ICH located in the brain stem.

Cryptogenic ICH was considered in 15% of our patients, 48% of them with ICH located in the lobar region. If we included those patients who had ICH of undetermined origin (6%), the number of patients in whom there was no definite cause of ICH was similar to that in other reported series.6,7,10,14,15

Pregnancy and the puerperium can be related to several types of stroke, including cerebral venous thrombosis. ICH occurs in from 1 to 5 per 10,000 pregnancies.35 Related mechanisms include aneurysmal and arteriovenous malformation rupture and hypertension. In this series, 7 women presented with ICH during the puerperium, and 1 during the third trimester of pregnancy was related to cerebral venous thrombosis. Seven patients had an ICH related to eclampsia. In 2 recently published population studies, the main causes of ICH were related to pregnancy and the puerperium, including preeclampsia/eclampsia and vascular malformation rupture.36,37 The frequency of cerebral venous thrombosis as a cause of ICH is poorly studied. In previously reported series of ICH in young people, this cause was not mentioned. In a series of patients with cerebral venous thrombosis associated with pregnancy and the puerperium, Cantú and Barinagarrementeria identified 7 with ICH among 67 patients with cerebral venous thrombosis.38 The functional prognosis was good in these patients and similar to that in a high percentage of patients with cerebral venous thrombosis.39

Use of sympathomimetic drugs was related to ICH in 7 patients (3.5%). ICH has been described after the use of amphetamine-like preparations; the most commonly implicated agent is phenylpropanolamine.40 Other drugs related to ICH include ephedrine, pseudoephedrine, and phencyclidine. Five of our patients had taken phenylpropanolamine, 1 ephedrine, and 1 an unspecified “nasal decongestant.” The real frequency of this complication is unknown. It has been estimated that as many as 5 billion doses of pills containing phenylpropanolamine are taken annually.41 The frequency of the relation of drug use to ICH is lower than reported by Toffol et al.,6 who found this association in 7% of their patients. This cause probably is not well recognized and should be routinely investigated in those patients with ICH with no usual risk factors.

Acute mortality in the present series was low compared with other series.5,6,12–14 There were no significant differences among the causes of ICH to explain the mortality rate. In the present series, the only distinction was a lower upper age limit of 40 years.

Several prognostic factors have been identified in previous studies of ICH, including the level of consciousness at presentation,42 hematoma size,43 and intraventricular extension.44 In the present series, the prognosis was poor in a univariate analysis that included hypertension as cause of ICH and ventricular extension, which was associated with the ICH located in the basal ganglia.

In summary, ICHs in young people are mainly lobar in location and mainly result from vascular malformations. Hypertension explains the majority of cases with a ganglionic location. Mortality and morbidity in the acute phase were low and related to hypertension as a cause of ICH.

Acknowledgment
We thank Carlos S. Kase, MD, Boston, Mass, for his suggestions and helpful criticism of this article.

References
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Stroke. 1999;30:537-541
doi: 10.1161/01.STR.30.3.537

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