Rate of Stroke Recurrence in Patients With Primary Intracerebral Hemorrhage

Michael D. Hill, MD, FRCPC; Frank L. Silver, MD, FRCPC; Peter C. Austin, PhD; Jack V. Tu, MD, PhD, FRCPC

Background and Purpose—Primary intracerebral hemorrhage (PICH) is a devastating illness with high early mortality. Hypertension is a major risk factor both for ischemic cerebrovascular disease and for intracranial hemorrhage. Survivors of PICH are at risk for both recurrent hemorrhage and ischemic cerebrovascular disease. We sought to determine the rate of recurrence of ICH or cerebral ischemia in a cohort of PICH patients at the Toronto Hospital, Toronto, Canada.

Methods—A retrospective search of computerized hospital records from 1986 to 1996 for patients with a discharge diagnosis of intracerebral hemorrhage (International Classification of Diseases, Ninth Revision–Clinical Modification [ICD-9-CM] code 431) was conducted to identify the index cases. Charts were abstracted for demographic and clinical characteristics. CT scans, MR scans, or radiologist reports were reviewed. To determine recurrence, the database was linked to the Ontario Provincial Government Vital Statistics Registry and to the Canadian Institute for Health Information database of hospital discharge abstracts. Logistic regression analysis was used to identify predictive factors for mortality after PICH. A Cox proportional hazards model was fitted to identify predictive factors for recurrent ICH or stroke.

Results—A total of 746 charts were identified by computer search. After abstraction, 423 index patients with PICH were identified. Of these, 27.4% died in the first 30 days of their admission. Predictors of death were age, intraventricular rupture of hemorrhage, and trilobar hemorrhage. The recurrence rate for PICH was 2.4% (95% CI 1.4% to 3.9%) per year, whereas the recurrence rate for ischemic cerebrovascular disease was 3.0% (95% CI 1.8% to 4.7%) per year. The only significant predictor of readmission for ICH was lobar location of the index hemorrhage, with a hazard ratio of 3.8 (95% CI 1.2 to 12.0).

Conclusions—PICH has a high 30-day mortality rate. Survival from the initial insult portends a moderate risk of recurrence of 2.4% per year for PICH and 3.0% per year for ischemic cerebrovascular disease. Patients with PICH are at risk for both ischemic stroke or TIA and recurrent hemorrhage; thus, PICH may be a marker for ischemic stroke. Patients with lobar hemorrhage have a 3.8-fold increased risk of recurrent ICH.

Key Words: intracerebral hemorrhage ■ amyloid ■ hypertension ■ cerebral ischemia

Approximately 10% of strokes are intracerebral hemorrhages,1 of which primary intracerebral hemorrhage (PICH), defined as spontaneous intracerebral hemorrhage (ICH) not attributable to an underlying cause (see below), is a subset. PICH is more often a devastating disease than ischemic stroke,2 with previous series noting a high early mortality rate ranging from 25% to 50% in the first 30 days. Among survivors, the rate of stroke recurrence after PICH has not been studied extensively. In patients with recurrent hemorrhage, lobar location of hemorrhage is a known predictor of recurrence.3 Cerebral amyloid angiopathy and hypertension are 2 of the major known risk factors for PICH.4 Cerebral amyloid angiopathy hemorrhage usually affects patients in their eighth decade and is typically lobar, rarely involving the deep subcortical nuclei.5 Hypertension is present in only 50% of patients with PICH in modern series. However, treatment of hypertension has had a major impact on the incidence of PICH over the past 50 years.6 We examined PICH at the Toronto Hospital over an 11-year period to try to establish the rate of recurrence. Because the decision to prescribe antiplatelet or anticoagulant therapy may be complicated by a past history of ICH, we were also interested in the recurrence rate of ischemic symptoms in patients with PICH.

Subjects and Methods

The neurology and neurosurgical services of the Toronto Hospital have a catchment area that includes the Greater Toronto area (4.4 million population) and much of the province of Ontario (11.1 million population). The study was performed in the Division of Neurology at the Toronto Western Hospital. Patients were identified if they had a hospital record from January 1, 1986, to December 31, 1996, with an International Classification of Diseases, Ninth Revision–Clinical Modification code 431 (intracerebral hemorrhage). The charts were reviewed to confirm the diagnosis. The 11-year period was divided into 2 groups: January 1, 1986, to December 31, 1988 (early) and January 1, 1989, to December 31, 1996 (late). All patients with nearly complete data sets were included in the study. Patients were excluded if they were younger than 18 years old, had a history of intracranial surgery, or had a diagnosis of intracranial hemorrhage at autopsy. Patients were divided into 2 groups: those with recurrent ICH and those with recurrent ischemic events. The groups were compared for demographic factors and clinical characteristics. The study was approved by the Research Ethics Board of the University of Toronto.

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123
PICH was defined as spontaneous ICH in the absence of secondary cause such as vascular malformation, vasculitis, moyamoya disease, aneurysm, cortical vein/sinus thrombosis, neoplasm, trauma, postoperative event, hyperviscosity syndrome, hemorrhagic diathesis, or ischemic stroke. PICH included patients with hypertension and with pathologically proven amyloid angiopathy. PICH was divided into lobar and nonlobar subtypes, which were defined anatomically. Nonlobar hemorrhage included ICH in which the epicenter of the hemorrhage was located in the putamen/caudate, thalamus, cerebellum, or brain stem, and lobar hemorrhage was defined as ICH located more peripherally, often extending to the brain surface. Lobar hemorrhages were divided by lobe (frontal, temporal, parietal, and occipital) or were named bilobar if 2 contiguous lobes were involved or trilobar if 3 or more lobes were involved.

The rate of miscoding of discharge diagnosis based on chart abstraction was 13.4%. One hundred charts were coded as ICH (ICD-9-CM code 431) when the true diagnosis was either subarachnoid hemorrhage (n=41) or other (n=59).

The analysis was then divided into 2 parts. Part 1 consisted of a descriptive analysis of the abstracted charts. Part 2 used existing provincial databases to determine the rate of recurrence of ICH among patients who survived their index hemorrhage.

All persons who die in Ontario must have a death certificate filed. The Ontario government vital statistics registry of death certificate data was searched for any surviving patients who had died. Data were available for date of death and cause of death according to the death certificate until November 1, 1998. The emigration rate from Ontario in 1996 was 0.2% of the population; the emigration rate was similarly low during the study period. These results were used in part 1 of the analysis to calculate overall mortality.

The Canadian Institute of Health Information (CIHI) database contains all hospital discharge information for Canadian patients. All residents of Ontario automatically have universal health insurance coverage under the provincial health insurance plan. Because of administrative changes in the plan, patients who were admitted with PICH before 1991 were unable to be linked to the CIHI database and were necessarily excluded from the follow-up analysis. Within these parameters, the CIHI database was searched for the occurrence of hospital readmission due to a diagnosis of ICH or a diagnosis of stroke or transient ischemic attack (TIA; ICD-9-CM codes 434, 435, and 436). The follow-up period was defined as the time from discharge for hospitalization due to the index hemorrhage until either readmission for recurrent PICH or cerebral ischemia, death, or March 31, 1998. The yearly rate of recurrence of ICH in surviving patients was determined. For reasons of patient confidentiality, the CIHI database is blinded. It was therefore not possible to further follow up recurrent cases by chart review or interview. The study was reviewed and approved by the Research Ethics Board of The Toronto Hospital.

Logistic regression analysis was performed in part 1 to identify predictors of death at 30 days and occurrence of multiple hemorrhage. The following variables were chosen a priori for this analysis: age, gender, history of hypertension, residence outside the city of Toronto, PICH type, PICH location, intraventricular extension of ICH, and craniotomy for decompression of ICH.

In part 2, a Cox proportional hazards model was fitted to determine whether index hemorrhage admission characteristics were predictive of the hazard of readmission for recurrent hemorrhage and for readmission for all types of cerebral ischemia. Each candidate predictor variable was screened in a univariate regression model. Only those variables that were significant at the 0.20 level were included in the final regression model.

Because some patients could not be linked to the CIHI database, 2 groups of patients were generated: those who could be matched and those who could not. Characteristics of these 2 groups were compared by χ² test or 2-tailed t test where appropriate. Statistical analysis was done with SPSS 7.5 software for Windows. The Cox proportional hazards model was fitted with SAS 6.12 software.

Results

Part 1

Medical records from 746 patients showed an ICD-9-CM discharge diagnosis code of 431 and were abstracted (Figure 1). Of these, 423 patients with PICH were identified and are described in Table 1. CT or MRI scans or reports were available for review in 93.9% of these cases. Half (49.6%) of the patients had a history of hypertension. Hypertension was correlated with nonlobar hemorrhage (P<0.01, r=0.67) but not 30-day survival, intraventricular rupture, or age.

Craniootomy for hematoma evacuation was performed on 48 patients (11.4%) as part of their emergent management. Pathology reports were available for 23. Amyloid angiopathy was diagnosed in 3, hematoma with unidentified cause in 19, and Alzheimer’s disease without proven amyloid angiopathy in 1. An additional 4 patients had pathologically proven
amyloid angiopathy based on previous hemorrhages that had occurred before the study period. All 7 patients with proven amyloid angiopathy had lobar hemorrhages.

Simultaneous multiple PICH, defined as PICH in 2 or more locations at admission, occurred in 7 patients. All the hemorrhages were lobar, but only 2 of these patients had biopsy-proven amyloid angiopathy. One patient was admitted to the hospital on 3 separate occasions, each time with multiple PICH. Logistic regression analysis confirmed lobar location of hemorrhage as the only significant predictor of multifocal hemorrhage at presentation (P < 0.011).

Patients 45 years old or younger made up 10.2% (n = 43) of the index patients. In this subpopulation, the male-to-female ratio was 2.9, with a mean age of 30.5 years. Only 32.6% of patients had a known history of hypertension. Mortality at 30 days was 14.0%. Similar to the total group, 44.2% of hemorrhages were lobar and 65.8% were nonlobar.

Three hundred seven patients with PICH survived to 30 days after their index hemorrhage, and long-term survival is shown in Figure 2. Predictors of 30-day mortality among 3 groups (the entire cohort, the subgroup of lobar hemorrhage, and the subgroup of nonlobar hemorrhage) were determined by logistic regression analyses and are described in Table 2.

Of 327 records without PICH, there were 191 ICHs with secondary causes (Table 3), 35 primary intraventricular hemorrhages, 41 subarachnoid hemorrhages, 59 miscoded charts without any form of ICH, and 1 chart without enough data to allow classification.

### Part 2

Of the 307 patients with PICH who survived to 30 days, 172 were used for the analysis of recurrence of PICH or cerebral ischemia. Excluded patients comprised 135 who were unable to be linked with the CIHI database. The mean ages of the unlinked and linked groups were 62.4 and 65.7 years, respectively (P = 0.037).

During a mean follow-up period of 3.6 years, 15 patients were admitted to an Ontario hospital with a diagnosis of ICH. The rate of recurrence of ICH was calculated at 2.4% per year (95% CI 1.4% to 3.9%). Of these 15 cases, the index PICH was lobar in 11 and nonlobar in 4. Similarly, the rate of readmission for cerebral ischemia after PICH was 3.0% per year (95% CI 1.8% to 4.7%). Of these 19 cases, the index PICH was lobar in 7 and nonlobar in 12 (Figure 1).
Risk of ICH recurrence among patients with lobar hemorrhage was also a significant predictor of multiple simultaneous hemorrhage. Although pathological tissue was examined in only a small number of cases, all cases with confirmed amyloid angiopathy were lobar in location. This is highly consistent with known information about amyloid angiopathy.

Recent reports suggest that recurrent hemorrhage due to hypertension may be more common than previously believed. In the present study, a history of hypertension was present in only 50% of cases. This is similar to or less than that reported in previous series, and it suggests that other undetermined factors (unmeasured in this study) are important in PICH, for example, acute rises in blood pressure and reperfusion. Even fewer young patients had a history of hypertension (32%). Part of this difference may represent PICH as the first manifestation of occult hypertension. Alternatively, factors that cause PICH in young patients may be more diverse or not easily identified (eg, microarteriovenous malformations). Identification of these factors is relevant, because the acute mortality rate in young patients is only 14%, leaving 86% at future risk for recurrence and potentially amenable to preventive measures in addition to treatment of hypertension.

The 30-day mortality rate of 25% and the predictors of 30-day mortality, such as age and intraventricular extension, confirm previous experience. They were robust measures of poor prognosis in both lobar and nonlobar subtypes of PICH. Other known predictors, such as hemorrhage volume and initial Glasgow coma score, were not evaluated in the present study. However, trilobar hemorrhage is probably a crude correlate of hematoma volume and was predictive of death in both the nonlobar hemorrhage group and the entire cohort. We suspect that the final predictive factor (in the lobar hemorrhage group only), location of residence outside the city of Toronto, represents a case-selection bias. More seriously ill patients, who are more likely to die, are more likely to be referred to our tertiary-care center. However, we cannot exclude the possibility that differences in the quality of care or transport time between community hospitals and tertiary hospitals affected outcome.

Interestingly, patients with PICH were slightly more likely to be readmitted to the hospital with ischemic cerebrovascular disease (3.0% per year) than with recurrent hemorrhage (2.4% per year). This has clear implications for management of secondary prevention. Anticoagulant therapy may be contraindicated in patients with lobar hemorrhage. Recent data support the concept that patients with amyloid angiopathy or leukoaraiosis are much more likely to develop ICH while undergoing anticoagulant therapy. The use of antiplatelet therapy in patients with past ICH remains controversial. Aspirin may increase the risk of ICH. However, the equivalence of rates of recurrence of both ischemic cerebrovascular disease and ICH in this group of patients suggests that PICH is a risk factor for ischemic stroke. Therefore, attention to known ischemic stroke risk factors (in addition to hypertension), such as hypercholesterolemia, is probably important. It remains uncertain whether antiplatelet agents should be used as primary ischemic stroke prevention in this

### TABLE 3. ICH With Secondary Etiology (n=191)

<table>
<thead>
<tr>
<th>Causes of Secondary ICH</th>
<th>n</th>
</tr>
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<tbody>
<tr>
<td>AVM or aneurysm</td>
<td>62</td>
</tr>
<tr>
<td>Hemorrhage into neoplasm (1 thrombocytopenic)*</td>
<td>31</td>
</tr>
<tr>
<td>Anticoagulation (2 into infarcts)</td>
<td>29</td>
</tr>
<tr>
<td>Hemorrhage into infarct (2 on heparin, 1 AVM gluing with embolism to sagittal sinus)*</td>
<td>29</td>
</tr>
<tr>
<td>Thrombocytopenia† (1 into a tumor)*</td>
<td>11</td>
</tr>
<tr>
<td>Postthrombolytic therapy</td>
<td>8</td>
</tr>
<tr>
<td>Trauma</td>
<td>6</td>
</tr>
<tr>
<td>Moyamoya disease</td>
<td>3</td>
</tr>
<tr>
<td>Acute hepatic failure</td>
<td>3</td>
</tr>
<tr>
<td>Leukemia</td>
<td>2</td>
</tr>
<tr>
<td>Hyperperfusion syndrome after endarterectomy</td>
<td>2</td>
</tr>
<tr>
<td>†aPTT of undetermined etiology</td>
<td>2</td>
</tr>
<tr>
<td>Other‡</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>191</td>
</tr>
</tbody>
</table>

AVM indicates arteriovenous malformation; aPTT, activated partial thromboplastin time.

*Parentheses indicate 5 cases double counted.
†Platelets <150.
‡Other: one each of venous sinus thrombosis, after biopsy for cytomegalovirus encephalitis, hemorrhage into a benign cyst; polycythemia rubra vera, Waldenstrom’s macroglobulinemia, acute hemorrhagic leukoencephalitis, hemophilia type A, and HELLP syndrome.

Univariate analysis using age, gender, history of hypertension, and hemorrhage type (lobar versus nonlobar) identified only lobar hemorrhage as a statistically significant predictor of readmission for recurrent ICH. This was confirmed in the multivariate analysis, and the relative hazard was 3.8 (95% CI 1.2 to 12.0) (P<0.02). A similar analysis that used readmission for cerebral ischemia as the end point revealed no statistically significant clinical predictors in the univariate or multivariate analyses.

### Discussion

The major finding of this study is that the rates of recurrent hemorrhage and recurrent ischemic stroke or TIA were approximately equal in the study population. In addition, the study quantified an annual risk of clinical recurrence of 2.4% after initial PICH and determined a nearly 4-fold increase in risk of ICH recurrence among patients with lobar hemorrhage.

Pathological evidence of recurrent ICH is controversial. Autopsy studies suggested that up to 25% of patients dying of ICH had had previous hemorrhages. However, a more recent study, in which amyloid angiopathy was an exclusion criteria, found no evidence of previous hemorrhage among 218 patients with PICH. Over 1 year of clinical follow up, 104 Italian patients with PICH and intraventricular hemorrhage had no recurrent events. A second study noted an absolute recurrence rate of 24% among 112 survivors of PICH. Thus, previous studies have been small and have yielded conflicting results.

Lobar location of the index hemorrhage was the only significant predictor of recurrence and increased the risk of recurrence by a factor of 3.8. This is similar to results in previous studies. Lobar hemorrhage was also the only factor predictive of multiple simultaneous hemorrhage. Although pathological tissue was examined in only a small number of cases, all cases with confirmed amyloid angiopathy were lobar in location. This is highly consistent with known information about amyloid angiopathy.

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group of patients, but this is potentially a testable hypothesis for a randomized trial.

Two potential biases in our study were due to incomplete linkage of our databases and data miscoding. We were unable to link 135 patients (44.0%) to outcome data in the CIHI database. Although comparison of the linked and unlinked groups yielded a statistically relevant result in a single variable (mean age), we believe that this difference is unlikely to be clinically important and does not detract from the study’s conclusions.

We relied on the coding of discharge diagnosis by medical records personnel to identify both index cases and recurrences. The rate of miscoding based on abstracted information was 13.4%. This may have resulted in overestimation of the true recurrence rate. However, the miscoding rate both is consistent with a previous study that compared a chart audit diagnosis with the medical record ICD-9-CM discharge diagnosis in 5 large US centers27 and is an intrinsic, largely unavoidable hazard of health services research.

At the same time, it is possible that reliance on hospital discharge abstracts for the diagnosis of ischemic stroke or TIA underestimates the true incidence. This would result in a conservative estimate of the recurrence rate. It is more likely that ICH is appropriately captured by hospital discharge data, because it tends to be less subtle in presentation.

In summary, we reviewed an 11-year experience at the Toronto hospital and determined that the rate of recurrence of ICH in Toronto is 2.4% per year and is approximately matched by a recurrence rate of ischemic cerebrovascular disease of 3.0% per year, which suggests that PICH is a marker for ischemic stroke.

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References
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