

Diabetes Is an Independent Risk Factor for In-Hospital Mortality From Acute Spontaneous Intracerebral Hemorrhage

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OBJECTIVE — We tested the hypothesis that diabetes is an independent determinant of outcome after intracerebral hemorrhage (ICH).

RESEARCH DESIGN AND METHODS — This was a hospital-based prospective study. The setting was an acute care 350-bed hospital in the city of Barcelona, Spain. Spontaneous ICH was diagnosed in 229 (11%) of 2,000 consecutive stroke patients included in a prospective stroke registry during a 10-year period. Main outcome measures were frequency of demographic variables, risk factors, clinical events, neuroimaging data, and outcome in ICH patients with and without diabetes. Variables related to vital status at discharge (alive or dead) in the univariate analysis plus age were studied in 4 logistical regression models.

RESULTS — A total of 35 patients (15.3%) had diabetes. The overall in-hospital mortality rate was 54.3% in the diabetic group and 26.3% in the nondiabetic group ($P < 0.001$). Previous cerebral infarction, altered consciousness, sensory symptoms, cranial nerve palsy, multiple topography of the hematoma, intraventricular hemorrhage, and infectious complications were significantly more frequent in diabetic patients than in nondiabetic patients. The presence of diabetes was a significant predictive variable in the model based on demographic variables and cardiovascular risk factors (odds ratio 2.98 [95% CI 1.37–6.46]) and in the models based on these variables plus clinical variables (5.76 [2.01–16.51]), neuroimaging variables (5.59 [1.87–16.69]), and outcome data (6.10 [2.04–18.29]).

CONCLUSIONS — Diabetes is an independent determinant of death after ICH. ICH in diabetic individuals presents some different clinical features compared with ICH in nondiabetic patients.

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Acute spontaneous intracerebral hemorrhage (ICH) is a serious disease with high mortality and morbidity (1–3). Multivariate studies that have investigated 30-day mortality after ICH have shown that the level of consciousness, size of the hematoma, ventricular extension, limb paresis, and communication disorders are independent predictors of death

(4–10). In a recent study, the age of the patient and the amount of alcohol consumed within 1 week of the ICH seemed to be independent determinants of outcome after ICH (11). However, besides the severity of hemorrhage, a few studies have analyzed the influence of preictal factors on the outcome of ICH. Whether diabetes (which increases mortality in ischemic stroke) (12),

other vascular risk factors, or previous or concomitant pathological conditions influence the outcome is unknown. Experimental studies have demonstrated that a zone of ischemia surrounds the hematoma, which is maximal when uncontained and when large volumes of blood are involved (13). Hyperglycemia in the acute phase of stroke has been established as a predictor of poor outcome in nondiabetic patients. Because both acute and chronic hyperglycemia are associated with increased edema and infarct size and with reduced cerebral blood flow and cerebrovascular reserve (12), one may postulate that diabetes may also increase ischemic brain damage around an ICH and therefore emerge as a clinical predictor of worse prognosis in ICH patients. The aim of this study was to determine the influence of diabetes on in-hospital mortality in a cohort of 229 consecutive ICH patients in a prospective stroke registry. Subjects with diabetes diagnosed before the present admission and subjects with diabetes who encountered the diagnosis after the stroke were both included.

RESEARCH DESIGN AND METHODS

Patients

Between January 1986 and December 1995, data on 2,000 acute stroke patients admitted consecutively to the Department of Neurology of Hospital del Sagrat Cor of Barcelona, Spain, were collected prospectively in a stroke registry (14). Our institution is an acute care 350-bed teaching hospital in the city of Barcelona and serves a population of ~250,000 people. All patients with cerebrovascular disease are initially attended to in the emergency department and are then admitted to the Department of Neurology, which has 25 beds and an acute stroke unit. Intensive care unit beds are also available. Patients are chosen for admission to the Department of Neurology if the reason for consultation is an acute cerebrovascular event occurring independently of the presence or absence of severe concomitant medical problems. Patients with transient ischemic

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Abbreviations: CT, computed tomography; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; OR, odds ratio; TIA, transient ischemic attack.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

attack (TIA) or reversible neurological deficits who are evaluated on an outpatient basis are routinely referred to the emergency department for assessment. Thus, the proportion of patients experiencing minor strokes who are not treated at the hospital is negligible. Subtypes of stroke were classified according to the Cerebrovascular Study Group of the Spanish Society of Neurology (15), which is similar to the National Institute of Neurological Disorders and Stroke classification (16) and has been used by our group in previous studies (14,17). Subtypes of stroke included TIA ($n = 239$), atherothrombotic stroke ($n = 452$), lacunar stroke ($n = 374$), cardioembolic infarction ($n = 347$), infarction of undetermined origin ($n = 224$), infarction of unusual cause ($n = 76$), ICH ($n = 229$), subarachnoid hemorrhage ($n = 35$), spontaneous subdural hematoma ($n = 23$), and spontaneous epidural hematoma ($n = 1$). For this study, the group of 229 patients with ICH was selected.

Methods

All patients were admitted to the hospital within 48 h of the onset of symptoms. On admission, demographic characteristics, salient features of clinical and neurological examinations, results of laboratory tests (blood cell count, biochemical profile, serum electrolytes, and urinalysis), chest radiography, and 12-lead electrocardiography were recorded. Neurological examination was performed on a daily basis. In all patients, a brain computed tomography (CT) scan was performed within this first week of hospital admission. Overall, 22% of patients were studied with magnetic resonance imaging (MRI) or angio-MRI. Other investigations included arterial digital subtraction angiography in 16% of patients, 2-dimensional echocardiography in 17%, and lumbar puncture in 5%. A documented medical diagnosis of diabetes was supported by chemical blood tests until the moment of inclusion in the study following the criteria of the National Diabetes Data Group (18).

For each patient, demographic data, vascular risk factors, clinical features, neuroimaging findings, and outcome were recorded. Demographic variables included age and sex. Anamnestic findings consisted of history of hypertension, diabetes, myocardial infarction or angina, rheumatic heart disease, congestive heart failure, atrial fibrillation, smoking (>20 cigarettes/day), alcohol abuse (>80 g/day), intermittent claudication, TIA, previous cerebral infar-

tion, hyperlipidemia, nephropathy, cirrhosis or chronic liver disease, chronic obstructive pulmonary disease, and age ≥ 85 years. As in a previous study (14), congestive heart failure, chronic obstructive pulmonary disease, liver disease, and atrial fibrillation were pooled under the single category of previous or concomitant pathological conditions. Clinical variables included sudden onset of symptoms (in minutes), headache, dizziness, seizures, nausea and vomiting, altered consciousness (drowsy, stuporous, or comatose), limb weakness (hemiparesis or hemiplegia, Babinski's sign not mandatory), sensory symptoms, aphasia or dysarthria, ataxia, cranial nerve palsy, and presence of lacunar syndrome (i.e., pure motor hemiparesis, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, and dysarthria ["clumsy hand"]) (19,20).

The region and total volume of hemorrhage were identified on the CT films. The total volume of parenchymal hemorrhage was estimated using the formula for an ellipsoid ($\frac{4}{3} \pi a \times b \times c$, where a , b , and c represent the respective radii in 3 dimensions). Other authors have already demonstrated that this estimated volume is very close to the actual hemorrhage volume measured by computerized image analysis (7,21). Neuroimaging variables in relation to the region of hemorrhage included the thalamus ($n = 31$), internal capsule and basal ganglia ($n = 49$), lobar ($n = 76$), cerebellum ($n = 15$), brainstem ($n = 15$), multiple topographical involvement ($n = 34$) (when more than one of the aforementioned topographies was affected by the hemorrhage), and primary intraventricular hematoma ($n = 9$). Secondary intraventricular blood expansion (evidence of intraventricular blood on CT and/or MRI scans) for each topography was also assessed.

Outcome variables included cardiac events (acute myocardial infarction, heart failure, or tachyarrhythmia), respiratory events (pulmonary embolism, atelectasis, or lower respiratory tract infection), vascular events, and infectious complications. Causes of death were analyzed according to the criteria of Silver et al. (22) The degree of clinical disability was evaluated according to the scale recommended by the Ad Hoc Committee (23).

Statistical analysis

Univariate analysis for each variable in relation to vital status at discharge (alive or dead); differences in the frequency of demographic characteristics, vascular risk factors,

clinical events, and neuroimaging data; and outcome between ICH patients with and those without diabetes were assessed with the Student's t test, the χ^2 test (with Yates correction when necessary), and the analysis of variance. Statistical significance was set at $P < 0.05$. Variables related to vital status at discharge on the univariate analysis plus age (used as a continuous variable with a constant odds ratio [OR] for each year) were subjected to multivariate analysis with a logistical regression procedure and forward stepwise selection when P was < 0.10 . In-hospital mortality coded as alive = 0 and dead = 1 was the dependent variable. A first predictive model was based on demographic and vascular risk factor variables (total of 7 variables). In addition to these variables, clinical variables dichotomized as present versus absent were included in the second model (total of 14 variables); clinical and neuroimaging variables (also dichotomized as present versus absent) were included in the third model (total 17 variables); and clinical, neuroimaging, and outcome variables were included in the fourth model (total of 30 variables). Statistically significant variables in the comparative analysis between ICH patients with and without diabetes were also subjected to multivariate analysis. The level of significance to remain in the model was 0.15, and the tolerance level was 0.0001 (24). The maximum likelihood approach was used to estimate weights of the logistical parameters (25). SPSS-PC+ (26) and BMDP (27) computer software programs were used for statistical analysis.

RESULTS — Of the 229 patients consecutively admitted for ICH, 35 (15.3%) had diabetes. The means \pm SD age of ICH patients was 70.5 ± 12.2 years, and 53% were men. The mean duration of hospital stay was 22.2 ± 24 days. The overall in-hospital mortality rate was 31% ($n = 70$). The mortality in nondiabetic patients was 26.3 vs. 54.3% in diabetic subjects ($P < 0.001$). Causes of death in the 70 ICH patients included cerebral herniation in 44, pneumonia in 8, sepsis in 8, sudden death in 3, myocardial infarction in 1, pulmonary thromboembolism in 1, and unknown cause in 5. In the 5 patients who died of unknown causes, autopsies were not performed.

In relation to the region of hemorrhage, the mortality rate was 65% in cases of multiple topographical involvement ($n = 22$) followed by 44% in primary intraventricular hematoma ($n = 4$), 40% in brainstem

ICH ($n = 6$), 25% in thalamic ICH ($n = 8$), 25% in lobar ICH ($n = 19$), 20% in cerebellar ICH ($n = 3$), and 16% in internal capsule–basal ganglia ICH ($n = 8$). Survivors were significantly younger than patients who died (69.07 ± 12.75 vs. 73.94 ± 10.32 years of age, respectively, $P < 0.001$). The overall mean survival time was 15 ± 23 days.

In the univariate analysis and in addition to diabetes, other variables significantly associated with outcome are shown in Table 1. After multivariate analysis, chronic liver disease, previous cerebral infarction, advanced age (≥ 85 years), altered consciousness, limb weakness, nausea and vomiting, intraventricular hemorrhage, and respiratory complications appeared to be independent clinical factors of in-hospital mortality in the logistical regression models (Table 2). Advanced age and diabetes, however, were consistently selected in the 4 models. On the other hand, in the 4 models, setting a cutoff point of 0.50 for predicting vital status at hospital discharge resulted in a sensitivity of 60, 79, 77, and 76%; a specificity of 72, 82, 87, and 88%; and a total correct classification of 71, 82, 84, and 86%, respectively. These percentages were not significantly improved by using an “optimal” cutpoint, as indicated by receiver operating characteristic curves (28).

Distinctive features of ICH patients with diabetes compared with subjects without diabetes included a significantly higher occurrence of previous cerebral infarction, altered consciousness, sensory symptoms, cranial nerve palsy, multiple topography for the hematoma, intraventricular hemorrhage, and infectious complications (Table 3). However, no statistically significant differences were evident between diabetic and nondiabetic subjects regarding mean length of hospital stay (20.2 ± 24.1 vs. 22.5 ± 24.1 days, respectively) and percentage of symptom-free patients at hospital discharge (5.7 vs. 3.1%, respectively). After multivariate analysis, previous cerebral infarction, cranial nerve palsy, and ICH of multiple topography appeared to be independent clinical factors of ICH in patients with diabetes (Table 4).

CONCLUSIONS — The present study was conducted to assess the influence of diabetes on in-hospital mortality in 229 consecutive patients with ICH collected in a prospective stroke registry. The study sample consisted of a hospital-referred population of patients admitted to an acute stroke unit and is therefore

Table 1—Results of a univariate analysis in 229 patients with ICH

Variable (coded)	Alive	Dead	P
<i>n</i>	159	70	
Sex			
Male	90 (73.8)	32 (26.2)	NS
Female	69 (64.5)	38 (35.5)	
Diabetes			
Absent	143 (73.7)	51 (26.3)	<0.001
Present	16 (45.7)	19 (54.3)	
Previous cerebral infarction			
Absent	151 (71.6)	60 (28.4)	<0.05
Present	8 (44.4)	10 (55.6)	
Chronic obstructive pulmonary disease			
Absent	155 (70.8)	64 (29.2)	<0.05
Present	4 (40.0)	6 (60.0)	
Chronic liver disease			
Absent	155 (70.8)	64 (29.2)	<0.05
Present	4 (40.0)	6 (60.0)	
Age ≤ 85 years			
Absent	145 (72.1)	56 (27.9)	<0.05
Present	14 (50.0)	14 (50.0)	
Nausea and vomiting			
Absent	129 (73.7)	46 (26.3)	<0.05
Present	30 (55.6)	24 (44.4)	
Dizziness			
Absent	140 (67.3)	68 (32.7)	<0.05
Present	19 (90.5)	2 (9.5)	
Altered consciousness			
Absent	116 (93.5)	8 (6.5)	<0.001
Present	43 (41.0)	62 (59.0)	
Limb weakness			
Absent	48 (92.3)	4 (7.7)	<0.001
Present	111 (69.8)	66 (37.3)	
Cerebellar signs			
Absent	141 (67.5)	68 (32.5)	<0.05
Present	18 (90.0)	2 (10.0)	
Cranial nerve palsy			
Absent	150 (71.8)	59 (28.2)	<0.05
Present	9 (45.0)	11 (55.0)	
Lacunar syndrome			
Absent	142 (67.0)	70 (33.0)	<0.01
Present	17 (100)		
Capsulo-ganglionic involvement			
Absent	118 (65.6)	62 (34.4)	<0.05
Present	41 (83.7)	8 (16.3)	
Brainstem hematoma			
Absent	150 (70.0)	64 (29.9)	0.01
Present	9 (60.0)	6 (40.0)	
Cerebellum involvement			
Absent	147 (68.7)	67 (31.3)	0.002
Present	12 (80.0)	3 (20.0)	
Thalamic hematoma			
Absent	136 (68.7)	62 (31.3)	0.002
Present	23 (74.2)	8 (25.8)	
Hematoma of multiple topography			
Absent	147 (75.4)	48 (24.6)	<0.001
Present	12 (35.3)	22 (64.7)	

(continued on page 1530)

Table 1—Continued

Variable (coded)	Alive	Dead	P
<i>n</i>			
Intraventricular hemorrhage			
Absent	130 (81.8)	29 (18.2)	<0.001
Present	29 (41.4)	41 (58.6)	
Cardiac events			
Absent	158 (70.2)	67 (29.8)	<0.05
Present	1 (25.0)	3 (75.0)	
Respiratory events			
Absent	154 (72.0)	60 (28.0)	<0.01
Present	5 (33.3)	10 (66.7)	
Vascular complications			
Absent	159 (70.0)	68 (30.0)	<0.05
Present		2 (100)	

Data are *n* (%).

potentially subject to referral bias. All patients underwent a standardized clinical, analytical, and radiological assessment, but additional investigations (as expected) were selective. We found that stroke patients with diabetes have a higher mortality rate, worse neurological outcome, and more severe disability than stroke patients without diabetes (29–36). In most studies, however, brain infarcts and ICH have been combined to form the category of “stroke,” which likely causes bias by either overestimation or underestimation of the significance of risk factors, clinical findings, and neuroimaging features for different stroke subtypes (37).

Little information exists on the characteristics and outcome of stroke in ICH patients with diabetes. In the study of Thurim et al. (38), the presence of diabetes did influence the outcome of parenchymatous hemorrhage. Our study shows a strong association between diabetes and in-hospital mortality in ICH. ICH diabetic patients had a significantly higher mortality rate, and we found diabetes to be a major determinant of death after ICH in the 4 logistical regression models analyzing demographic and vascular risk factors (OR 2.98); demographic variables, vascular risk factors, and clinical variables (OR 5.76); demographic variables, vascular risk factors, clinical data, and neuroimaging variables (OR 5.59); and demographic variables, vascular risk factors, clinical data, neuroimaging variables, and outcome (OR 6.10). In a prospective hospital-based study in Asia in which 783 patients with ICH were included, diabetes was also a risk factor for early death (OR 1.74) (39).

We found that, in ICH patients, diabetes was associated with the presence of hematoma of multiple topography (OR 3.74), cranial nerve palsy (OR 3.55), and

previous cerebral infarction (OR 3.36), three factors that can be associated with a higher in-hospital mortality.

On the other hand, little is known about the influence of diabetes on the volume of damaged brain tissue in ICH patients. In the present study, ICH of multiple topography was significantly more frequent in diabetic than in nondiabetic patients, and, in a previous report (40), diabetic patients with hemorrhagic stroke had a larger hematoma size than patients without diabetes. In different studies (6,21), hemorrhage volume was the best predictor of mortality for all locations of spontaneous ICH. Diabetes is known to produce deleterious effects on the microvasculature (41) that may result in increased risk for multiple topography bleeding. The ICH of multiple topography in patients with diabetes may be related to the specific angiopathy induced by diabetes in small vessels. The vasculopathy of perforating cerebral arteries (the walls of which are weakened by lipid and hyaline material

Table 2—Independent predictive value of different variables on in-hospital mortality

Statistical model based on	β	SE (β)	OR (95% CI)
Demographic and vascular risk factor variables*			
Chronic liver disease	1.4831	0.6878	4.41 (1.15–16.96)
Previous cerebral infarction	1.2542	0.5237	3.51 (1.26–9.78)
Age ≥85 years	1.2255	0.4264	3.41 (1.48–7.86)
Diabetes	1.0905	0.3957	2.98 (1.37–6.46)
Demographic, vascular risk factor, and clinical variables†			
Altered consciousness	3.0368	0.4581	20.84 (8.49–51.14)
Limb weakness	2.1943	0.6371	8.97 (2.57–31.28)
Diabetes	1.7506	0.5375	5.76 (2.01–16.51)
Nausea and vomiting	1.2646	0.4716	3.54 (1.41–8.92)
Age ≤85 years	1.2424	0.5697	3.46 (1.13–10.58)
Demographic, vascular risk factor, clinical, and neuroimaging variables‡			
Altered consciousness	2.7721	0.4707	15.99 (6.36–40.23)
Limb weakness	2.2327	0.6458	9.33 (2.63–33.06)
Diabetes	1.7209	0.5583	5.59 (1.87–16.69)
Age ≥85 years	1.2259	0.5664	3.41 (1.12–10.34)
Nausea and vomiting	1.0770	0.4880	2.94 (1.13–7.64)
Intraventricular hemorrhage	0.8277	0.4173	2.29 (1.01–5.18)
Demographic, vascular risk factor, clinical, neuroimaging, and outcome variables§			
Altered consciousness	2.9118	0.4988	18.39 (6.92–48.88)
Limb weakness	2.0933	0.6506	8.11 (2.27–29.04)
Diabetes	1.8091	0.5598	6.10 (2.04–18.29)
Respiratory complications	1.7971	0.7661	6.03 (1.34–27.08)
Age ≥85 years	1.2441	0.5738	3.47 (1.13–10.68)
Nausea and vomiting	1.1671	0.4990	3.21 (1.21–8.54)

*β = -1.3723 ± 0.1968, goodness-of-fit χ^2 = 0.2954, df = 2, P = 0.8627; †β = -5.3481 ± 0.7987, goodness-of-fit χ^2 = 5.3252, df = 6, P = 0.5028; ‡β = -5.4596 ± 0.8147, goodness-of-fit χ^2 = 9.4786, df = 7, P = 0.2201; §β = -5.6009 ± 0.8340, goodness-of-fit χ^2 = 12.0699, df = 7, P = 0.0983.

Table 3—Comparison of data for the 229 patients with ICH

Variable	Without diabetes	With diabetes	P
Total patients	194 (52.6)	35 (15.3)	
Sex (M)	102 (52.6)	20 (57.1)	NS
Age (years)	70.13 ± 12.64	72.5 ± 9.8	NS
Previous cerebral infarction	12 (6.2)	6 (17.1)	0.05
Altered consciousness	84 (43.3)	21 (60.0)	0.07
Sensory symptoms	93 (47.9)	23 (65.7)	0.06
Cranial nerve palsy	13 (6.7)	7 (20)	0.05
Hematoma of multiple topography	22 (11.3)	12 (34.3)	0.001
Intraventricular hemorrhage	54 (27.8)	16 (45.7)	0.05
Infectious complications	35 (18.0)	11 (31.4)	0.07

Data are n (%) or means ± SD.

[lipohyalinosis and fibrinoid necrosis]), microaneurysms, and/or microangiopathy (42) may be a real risk of hematoma of multiple topography in diabetic patients. These changes in cerebral vessels would perhaps make diabetic patients more prone than nondiabetic patients to develop hemorrhages of a large size.

Possible causes for our finding of a significantly higher occurrence of cranial nerve palsy in diabetic versus nondiabetic patients with ICH include increased intracranial pressure and compression of the diencephalon and brainstem. These are clinical situations associated with a worse neurological outcome (43).

In the study by Juvela (44), 7% of men with ICH and 3% of women with ICH presented with previous brain infarction. In our study, previous cerebral infarction was a predictor of ICH patients with diabetes. This may be explained by an association between diabetes and carotid artery intimal-medial thickness (a form of asymptomatic carotid artery disease), between diabetes and a high frequency of extracranial carotid artery stenosis and a more diffuse atherosclerotic disease, and between diabetes and an increased prevalence of atherogenic risk factors, notably hypertension, obesity, and abnormal blood lipids. All of these are risk factors of cerebral infarction (37,41).

Perilesional ischemia in brain regions surrounding the ICH has been recently reported and may be another possible contributor to poor outcome (45). In the first 24 h after an ICH, an ischemic zone with reduced metabolism is present in areas contiguous to the ICH. Severe regional cerebral blood flow reduction can eventually progress to infarction and may contribute to poor outcome (46,47). Early hematoma expansion, which occurs in 30% of patients (48,49), is the main cause of clinical deterioration during the hyperacute phase of ICH. Another possible mechanism for early ICH enlargement may result primarily from secondary bleeding into necrotic and congested perilesional tissue (which is more extensive in diabetic patients because of the effect of hyperglycemia) rather than continued bleeding at the initial site of arteriolar rupture.

In our study, as in others (4,31,50–55), chronic liver disease, age ≥85 years, altered consciousness, limb weakness, nausea and vomiting, intraventricular hemorrhage, and respiratory complications were also independent predictors of in-hospital mortality in ICH patients.

In conclusion, clinical factors indicative of the severity of ICH available at stroke onset have a predominant influence on in-hospital mortality and may help clinicians to assess prognosis more accurately. Dia-

betes is an important risk factor for mortality after an ICH. ICH in diabetic patients presents some differential clinical features from ICH in nondiabetic patients; accordingly, this subgroup of stroke patients should be very closely monitored.

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Table 4—Independent predictors of poor outcome associated with ICH in patients with diabetes

Variable	β	SE (β)	OR (95% CI)
Hematoma of multiple topography	1.3201	0.4487	3.74 (1.55–9.02)
Cranial nerve palsy	1.2658	0.5425	3.55 (1.22–10.27)
Previous cerebral infarction	1.2128	0.5744	3.36 (1.09–10.37)

β = −2.3023 ± 0.2592, goodness-of-fit $\chi^2 = 0.1483$, df = 1, P = 0.7001.

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