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Diabetes and intracerebral hemorrhage: Baseline characteristics and mortality

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ABSTRACT

Background: Acknowledging the conflicting evidence of diabetes as a predictor of short- and long-term mortality following an intracerebral hemorrhage (ICH), we compared baseline characteristics and 30-day and long-term mortality between patients with and without diabetes after an ICH—paying special attention to differences between type 1 (T1D) and type 2 (T2D) diabetes.

Methods: Patients with a first-ever ICH were followed for a median of 2.3 years. Adjusting for demographics, comorbidities and documented ICH characteristics increasing mortality after ICH, logistic regression analysis assessed factors associated with case-fatality and 1-year survival among the 30-day survivors. Diabetes was compared to patients without diabetes in separate models as (1) any diabetes and (2) T1D or T2D.

Results: Of our 969 patients, 813 (83.9%) had no diabetes, 41 (4.2%) had T1D, and 115 (11.9%) T2D. Compared to patients without diabetes, those with diabetes were younger, more often men, and had more frequently hypertension, coronary heart disease, and chronic kidney disease (CKD)—with similar ICH characteristics. T1D-patients were younger, had more often CKD and brain-stem ICH, and less often atrial fibrillation and lobar ICH, than did patients with T2D. Diabetes had no impact on case-fatality. Any diabetes (OR 2.42, 1.19-4.93), T1D (5.27, 0.95-29.28), and T2D (OR 2.20, 1.04-4.67) were independently associated with 1-year mortality.

Conclusions: ICH patients with diabetes exhibit a distinct pattern of comorbidities and disease characteristics with specific differences between T1D and T2D. Despite their younger age, T1D seems to carry a substantially higher likelihood for long-term mortality after an ICH than do T2D.

Introduction

Non-traumatic intracerebral hemorrhage (ICH) is the second most common and the most devastating type of stroke, causing 6% of all deaths globally [1]. Patients surviving from ICH seem to be at considerable risk of recurrent stroke, particularly non-fatal and fatal ICH [2]. The rate of recurrent ICH for early survivors in largely hospital-based studies differ between 1.3 to 7.4% per year [3].

A recent meta-analysis including 122 longitudinal studies reported a 1-year mortality of 54% and 5-year mortality of 71% after an ICH [3]. Diabetes is common in patients suffering from acute stroke and related to a worse outcome in ischemic stroke [4, 5]. However, the association between diabetes and ICH outcome remains controversial [3, 6-8]. Importantly, studies on features and prognosis of ICH in patients with type 1 (T1D) and type 2 diabetes (T2D) as different entities are virtually absent.

We aimed to compare ICH features between non-diabetic patients and patients with either T1D or T2D. Furthermore, we explored diabetes as a risk factor for case-fatality and long-term mortality during follow-up in these patients.

Methods

This retrospective observational study was performed at the Department of Neurology, Helsinki University Hospital (HUU). All required institutional permissions to perform the study were obtained. However, based on the Finnish legislation, formal approvals from local ethics committees or patient consents are not required in retrospective studies. Thus we were able to include all consecutive ICH cases.

We combined two ICH databases. The Helsinki ICH Study (HICHS) registry included all consecutive patients with non-traumatic ICH treated in the Department of Neurology, HUU, from January 1st2005 to March 31st 2011 as previously described [9]. The second dataset included all patients with ICH from the

nationwide Finnish Diabetic Nephropathy (FinnDiane) study database from 1997 to 2011. The FinnDiane Study is an ongoing, nationwide, prospective multicenter study seeking risk factors for diabetic complications of T1D [10]. Briefly, patients with ICH were identified from the FinnDiane database, death certificates, and the National Hospital Discharge Register based on the ICD-10. Medical records, computed tomography (CT), and magnetic resonance (MR) images of these patients were also obtained. Based on the medical files, brain images, and autopsy findings, two stroke neurologists (J.P. and R.L.) classified all events. A neuroradiologist was consulted if needed. Pooling the datasets allowed enriching the study population in both major subtypes of diabetes. Treatment of all patients followed published guidelines [11].

We excluded from both datasets epidural and subdural hematomas and ICH due to trauma, tumor, hemorrhagic transformation of ischemic stroke, and intracerebral clots in the setting of primary subarachnoid hemorrhage. Patients with a history of ICH and those dying prior to hospitalization without brain imaging were also excluded (Figure 1).

The eGFR was calculated with the Chronic Kidney Disease (CKD) Epidemiology Collaboration formula [12]. CKD was defined as eGFR <60 mL/min/1.73 m², or if the patient was undergoing dialysis or had undergone kidney transplantation.

Long-term mortality data of all patients were obtained from the Finnish Causes of Death Register, up to October 2011 for the HICHS and up to September 2011 for FinnDiane. Since follow-up time varied from 0 to 14.6 years in the T1D group, the maximum follow-up was truncated at 6.81 years, which was the longest follow-up for non-diabetic and patients with T2D. Based on the Finnish legislation, patient consent for registration was not required in a retrospective study and all consecutive cases were included.

Statistical analyses. Normality of continuous variables was tested and since all continuous variables were non-normally distributed, these are presented as median and interquartile range (IQR). Missing values for each parameter were reported. Differences between groups were analyzed with Mann-Whitney *U* test, χ^2 test, and Fisher's exact test, when appropriate. Longitudinal data were analyzed with Kaplan-Meier survival curves with Log rank tests. Life tables function was used to calculate cumulative 1-year and 5-year risks with 95% confidence intervals (CI). Whether diabetes was associated with case fatality was explored with binary logistic regression models. We first adjusted the model for age, sex, admission Glasgow Coma Scale score, ICH volume, infratentorial location, and intraventricular extension of hematoma, i.e. the known prognosticators of short-term mortality after ICH [13]. Second, the same model was adjusted for baseline comorbidities and medication differing between patients with and without diabetes, with a $P < 0.1$. For long-term mortality analysis, patients dying within the first 30 days were excluded. Proportionality assumption was tested for categorical variables with log minus log curves. Since the assumption did not hold for hypertension, coronary heart disease, and atrial fibrillation, we decided to analyze factors associated with

survival of at least 1 year with a logistic regression model. Patients staying alive with follow-up less than 1 year were censored from that analysis. As for case fatality, the model was first adjusted for demographics and factors with most consistent association with ICH mortality. Second, the same model was adjusted for chronic comorbidities differentiating patients with and without diabetes (hypertension, coronary heart disease, atrial fibrillation, and CKD). Diabetes was first analyzed as any diabetes, and, since there was a significant association, also as T1D or T2D in separate models with patients without diabetes as a reference. Odds ratios (OR) and 95% CI were reported. All analyses used SPSS Statistics 24 for Macintosh (SPSS, Armonk, N.Y., USA).

Results

We pooled 813 patients without diabetes, 41 patients with T1D and 115 T2D from two databases (Figure 1). Patients with diabetes were younger compared to patients without diabetes (Table 1). They were predominantly men, had more often hypertension, coronary heart disease and CKD, and were treated with antiplatelets and statins. No difference emerged in prior ischemic strokes or ICH characteristics between patients with and without diabetes (Table 1).

Patients with T1D were younger at the time of the ICH compared to patients with T2D (Table 2). Atrial fibrillation was detected in a larger proportion of patients with T2D in comparison to patients with T1D, and consequently T2D patients had used more frequently VKAs. Patients with T1D had more often CKD compared to those with T2D. Furthermore, patients with T1D had more often brain-stem ICH but less often lobar ICH, than did patients with T2D (Table 2).

Median follow-up time was 2.3 (IQR 0.2-4.2) years. Case fatality was 34.6% for patients without diabetes, 38.5% for patients with T1D, and 45.0% for patients with T2D ($P=0.160$). At 1 year, cumulative mortality was 34.0% (95% CI 30.1-37.9%) for patients without diabetes, 44.0% (28.3-59.7%) for T1D, and 45.0% (35.2-54.8%) for T2D. At the end of the follow-up period, 340 patients without diabetes (cumulative mortality at 5-years 46.0%, 95% CI 42.1-49.9%) and 82 patients with diabetes (56.0%, 48.2-63.8%) had died (20 patients with T1D, 51.0%, 35.3-66.7%; 62 patients with T2D, 58.0%, 48.2-67.8%). In the bivariate Kaplan-Meier analysis over the entire follow-up period, those with diabetes had higher mortality compared to patients without diabetes ($P=0.021$), with a trend-like difference ($P=0.051$) between the diabetes subtypes (Figure 2).

In the logistic regression analysis on case-fatality, we found no association with diabetes after adjusting for known mortality prognosticators in ICH, nor after further adjustment for comorbidities and medications prior to ICH (Table 3). Of interest, CKD—being by far most prevalent among patients with T1D—remained independently associated with case fatality.

In the first logistic regression analysis on 1-year survival, increasing age and any diabetes (OR 2.42, 95% CI 1.19-4.93; $P=0.015$) were associated with 1-year mortality (Supplemental Table). In the same model with diabetes subtypes included, T2D was associated with 1-year mortality, while T1D showed a trend ($P=0.057$) (Table 4). After further adjusting for comorbidities, the strength of association between any diabetes and 1-year mortality slightly increased (OR 2.57, 95% CI 1.19-5.52) (Supplemental Table). Comparing T1D and T2D with patients without diabetes, T1D demonstrated statistically approximately 3-fold stronger association with 1-year mortality than T2D in this model (Table 4).

Due to their strong inter-correlation, we further explored the effect of concomitant diabetes and CKD on mortality in the fully adjusted logistic regression models using interaction term diabetes x CKD. For both case-fatality and 1-year mortality, the interaction term remained non-significant in the models ($P=0.783$ and $P=0.714$, respectively), however.

Discussion

In this study we showed that demographic and comorbidity profiles differed in ICH patients with diabetes compared to patients without diabetes and further between the main diabetes subtypes, T1D and T2D. We also demonstrated that diabetes *per se* did not alter case fatality after ICH, albeit CKD was independently associated with worse early survival after ICH. Importantly, in 30-day survivors, both T1D and T2D remained independently associated with higher 1-year mortality even after adjusting for comorbidities and known factors associated with ICH mortality.

Several studies have investigated the role of diabetes as a risk factor for short- and long-term mortality after an ICH event [3]. One study showed higher short-term (in-hospital) mortality for ICH patients with diabetes compared to those without [14]. In contrast, no independent association between diabetes and 30-day mortality was observed in a large prospective study from Sweden or a nationwide study from South Korea [15, 16].

We have earlier shown diabetes to be independently associated with long-term mortality in young patients suffering from an ICH event [17]. Similarly, a prospective population based study from Sweden reported diabetes to be an independent risk factor for mortality in 1-year ICH survivors during a follow-up period of up to 13 years [18]. On the contrary, a registry study from the UK did not report diabetes to influence the outcome 1 to 10 years after an ICH, although it predicted a worse outcome after an ischemic stroke [19]. In view of the contradictory data of small scale studies, a systematic review and meta-analysis was recently published reporting a modest association between diabetes and ICH outcome [20]. Our results, however, show that even after adjusting for key confounders, mortality remains higher in particular for patients with T1D during long-term follow-up.

Admission hyperglycemia with or without diabetes diagnosis has been linked to a poorer outcome after stroke in both experimental and clinical settings [21, 22]. We have previously shown that this link only holds true if the admission hyperglycemia persists into the first days of the hospital admission, irrespective of coexisting diabetes [23]. Such persistent hyperglycemia is common in the absence of diabetes highlighting the theory of high blood glucose being reflective of the severity of the event (e.g. stress-induced hyperglycemia). Our results, suggest that also chronic hyperglycemia in the form of diabetes associated with long-term outcome after an ICH, on top of the stress-induced hyperglycemia reported earlier.

There were no significant differences in ICH volume, presence of ventricular hemorrhage, or distribution between supratentorial and infratentorial ICH location between patients with or without diabetes or between T1D and T2D. Yet, among the supratentorial location, deep ICHs were much more common in T1D patients and among the infratentorial location, brainstem ICHs were more frequent in T1D. We previously showed that microvascular diabetic complications, such as nephropathy and retinopathy, are risk factors for ICH in T1D patients [10]. This suggests that apart from known diabetic microvascular complications, also acute ICH could appear among the range of diabetic microangiopathic endpoints manifesting. Moreover, our findings also highlight the importance of studying different types of diabetes (T1D and T2D) as separate entities. This is of special interest knowing that the fate of patients with T2D is related to a number of atherogenic risk factors such as dyslipidemia, hypertension, and insulin resistance, whereas CKD seems to be the key driver of mortality in T1D [24]. However, the present results suggest that in 30-days survivors of ICH both subtypes of diabetes *per se* are associated with increased long-term mortality, with about 3-times higher risk for T1D. Furthermore, CKD was associated with 30-day mortality whereas both types of diabetes were associated with 1-year mortality. We further examined the effect of concomitant diabetes and CKD on both 30-day and 1-year mortality observing however non-significant interaction terms.

Some limitations of our study should be acknowledged. The patient population consisted of two different cohorts. Due to the fact that the number of patients with T1D was small (n=13) in the first data set (Department of Neurology at HUH) we included 28 patients with T1D from the FinnDiane cohort. Although we cannot rule out the possibility of differences between these patients from two different cohorts and cannot thus assess the effect size, we would like to stress the fact that the diagnosis of T1D was similar in both groups. Furthermore, the geographical distribution of the patients in the FinnDiane study resembles the general population in Finland and the response rate has been high. Therefore, a significant bias between the patients in these cohorts seem unlikely. The patients included at the HUH were from one university center whereas the FinnDiane ICH patients were treated at hospitals throughout Finland. Although general policy is to provide uniform health care for all citizens in Finland following guidelines, we cannot fully exclude the possibility of differences in treatment modalities between centers. We acknowledge the limitation not to have

data on DNR orders to predict its role for short-term mortality. Neither was information on surgical treatments available to include in the analysis. The follow-up time differed between the cohorts, but this limitation was overcome by using 6.81 years for truncation of the follow-up time. Finally, since violation of proportionality assumption was noted for several variables, we constructed a logistic regression to analyze long-term mortality (i.e. survival at 1 year) instead of a more conventional Cox proportional hazards analysis.

To summarize, based on our data diabetes raises the risk for death in the long-term after ICH even after controlling for important confounders. This was true also for patients with T1D although that they were markedly younger, emphasizing the high-risk profile in this patient group.

Disclosure of conflicts of interest

A.M. has received speaker's honoraria from Boehringer-Ingelheim and Stryker, and consulted for Boehringer-Ingelheim, Stryker, and Nestle. P-H.G. has received lecture fees from Astra Zeneca, Boehringer-Ingelheim, Eli Lilly, Genzyme, MSD, Novartis, Novo Nordisk, and Sanofi. He is an advisory board member of Abbvie, Astra Zeneca, Boehringer-Ingelheim, Cebix, Eli Lilly, Janssen, MSD, and Novartis. R.L.: none, D.G.: none, T.T.: none, L.M.T.: none, S.H-H.: none, C.F.: none, D.S.: none, J.P.: none.

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Table 1. Baseline characteristics of ICH patients with and without diabetes.

Variable (missing values, if any)	Patients without diabetes (n=813)	Patients with diabetes (n=156)	<i>P</i>
Age at ICH, years	68.7 (58.1-78.6)	64.2 (55.4-74.6)	0.003
Male sex	449 (55.2)	105 (67.3)	0.005
Hypertension	480 (59.0)	135 (86.5)	<0.001
Atrial fibrillation (4)	104 (12.9)	28 (17.9)	0.090
Prior ischemic stroke	73 (9.0)	19 (12.2)	0.212
Coronary heart disease (1)	89 (10.9)	36 (23.2)	<0.001
Chronic kidney disease (23)	95 (12.0)	53 (34.9)	<0.001
Prior antiplatelet treatment (4)	188 (23.1)	74 (48.7)	<0.001
Prior VKA treatment (6)	99 (12.2)	26 (17.0)	0.107
Prior statin treatment (10)	130 (16.1)	56 (37.1)	<0.001
Baseline ICH volume, mL (17)	9.5 (3.6-26.5)	9.2 (3.6-26.5)	0.989
Supratentorial location	700 (86.1)	127 (81.4)	0.129
Lobar	306 (37.6)	52 (33.3)	0.308
Infratentorial location	113 (13.9)	29 (18.6)	0.129
Brainstem	58 (7.1)	12 (7.7)	0.805
Cerebellum	63 (7.7)	19 (12.2)	0.069

Intraventricular hemorrhage	325 (40.0)	73 (46.8)	0.113
GCS at admission, points	15 (11-15)	14 (9-15)	0.065

Data are median (interquartile range) or n (valid %).

VKA = vitamin K antagonist; ICH = intracerebral hemorrhage; GCS = Glasgow Coma Scale.

Table 2. Comparison of baseline characteristics of ICH patients with type 1 and type 2 diabetes.

Variable (missing values, if any)	Type 1 diabetes (n=41)	Type 2 diabetes (n=115)	<i>P</i>
Age at ICH, years	49.4 (43.3-56.3)	67.7 (62.3-76.3)	<0.001
Male sex	28 (68.3)	77 (67.0)	0.876
Hypertension	36 (87.8)	98 (85.2)	0.683
Atrial fibrillation	1 (2.4)	27 (23.5)	0.003
Prior ischemic stroke	3 (7.3)	16 (13.9)	0.405
Coronary heart disease (1)	7 (17.1)	29 (25.4)	0.277
Chronic kidney disease (4)	30 (73.2)	23 (20.7)	<0.001
Prior antiplatelet treatment (4)	19 (51.4)	55 (47.8)	0.709
Prior VKA treatment (3)	1 (2.6)	25 (21.9)	0.005
Prior statin treatment (5)	12 (31.6)	44 (38.9)	0.417
Baseline ICH volume, mL (2)	6.6 (2.7-21.3)	9.8 (3.9-27.8)	0.184
Supratentorial location	31 (75.6)	96 (83.5)	0.266
Lobar	5 (12.2)	47 (40.9)	0.001
Infratentorial location	10 (24.4)	19 (16.5)	0.266
Brainstem	7 (17.1)	5 (4.3)	0.015
Cerebellum	5 (12.2)	14 (12.2)	1.000
Intraventricular hemorrhage	20 (48.8)	53 (46.1)	0.767
GCS at admission, points	14 (7-15)	14 (10-15)	0.789

Data are median (interquartile range) or n (valid %).

VKA, vitamin K antagonist; ICH, intracerebral hemorrhage; GCS, Glasgow Coma Scale.

Table 3. Logistic regression models exploring the association of baseline characteristics on 30-day mortality after intracerebral hemorrhage (ICH).

	Beta	Wald	Odds ratio (95% confidence interval)	P
Model 1 (n=952):				
Age at ICH, per year	0.03	16.36	1.03 (1.02-1.05)	<0.001
Male sex	0.60	8.99	1.82 (1.23-2.69)	0.003
Diabetes	0.27	1.19	1.31 (0.81-2.13)	0.276
Baseline ICH volume, per mL	0.03	55.25	1.03 (1.02-1.04)	<0.001
GCS at admission, per point	-0.24	94.20	0.79 (0.75-0.83)	<0.001
Infratentorial location	0.93	13.13	2.53 (1.53-4.18)	<0.001
Intraventricular hemorrhage	0.83	18.76	2.30 (1.58-3.35)	<0.001
Model 2 (n=914):				
Age at ICH, per year	0.02	6.50	1.02 (1.01-1.04)	0.006
Male sex	0.52	6.33	1.69 (1.12-2.54)	0.012
Diabetes	-0.09	0.09	0.92 (0.53-1.60)	0.765
Hypertension	0.18	0.62	1.19 (0.77-1.85)	0.433
Coronary heart disease	0.25	0.64	1.28 (0.70-2.34)	0.423
Atrial fibrillation	0.12	0.10	0.89 (0.42-1.89)	0.758
Chronic kidney disease	0.54	4.18	1.71 (1.02-2.87)	0.041
Prior antiplatelet treatment	-0.10	0.16	0.91 (0.56-1.48)	0.690
Prior VKA treatment	1.03	6.85	2.81 (1.30-6.09)	0.009
Prior statin treatment	-0.06	0.05	0.94 (0.55-1.62)	0.827
Baseline ICH volume, per mL	0.03	50.20	1.03 (1.02-1.04)	<0.001
GCS at admission, per point	-0.23	84.53	0.79 (0.75-0.83)	<0.001
Infratentorial location	0.98	13.61	2.67 (1.58-4.50)	<0.001
Intraventricular hemorrhage	0.84	17.29	2.31 (1.56-3.42)	<0.001

GCS, Glasgow Coma Scale; VKA, Vitamin K antagonist.

Table 4. Logistic regression models exploring the association of baseline characteristics on 1-year mortality in 30-day survivors of intracerebral hemorrhage (ICH). Model 1 includes known ICH prognosticators and diabetes subtypes. Model 2 includes known ICH prognosticators, diabetes subtypes, and comorbidities.

	Beta	Wald	Odds ratio (95% confidence interval)	P
Model 1 (n=654):				
Age at ICH, per year	0.10	43.34	1.10 (1.08-1.15)	<0.001
Male sex	0.36	1.46	1.44 (0.80-2.59)	0.228
Type 1 diabetes vs. no diabetes	1.66	3.61	5.27 (0.95-29.28)	0.057
Type 2 diabetes vs. no diabetes	0.79	4.26	2.20 (1.04-4.67)	0.039
Baseline ICH volume, per mL	0.01	1.88	1.01 (1.00-1.03)	0.170
GCS at admission, per point	-0.06	1.39	0.94 (0.85-1.04)	0.239
Infratentorial location	-1.44	3.73	0.24 (0.06-1.02)	0.053
Intraventricular hemorrhage	0.39	1.64	1.48 (0.81-2.71)	0.200
Model 2 (n=644):				
Age at ICH, per year	0.11	40.00	1.11 (1.08-1.15)	<0.001
Male sex	0.31	1.01	1.36 (0.75-2.47)	0.315
Type 1 diabetes vs. no diabetes	1.95	4.41	7.04 (1.14-43.48)	0.036
Type 2 diabetes vs. no diabetes	0.84	4.24	2.32 (1.04-5.17)	0.039
Hypertension	-0.09	0.08	0.91 (0.48-1.75)	0.784
Coronary heart disease	0.16	0.15	1.17 (0.53-2.60)	0.701
Atrial fibrillation	0.07	0.03	1.07 (0.48-2.39)	0.860
Chronic kidney disease	-0.33	0.68	0.72 (0.32-1.59)	0.411
Baseline ICH volume, per mL	0.01	1.75	1.01 (1.00-1.03)	0.186

GCS at admission, per point	-0.06	1.53	0.94 (0.85-1.04)	0.216
Infratentorial location	-1.50	3.90	0.22 (0.05-0.99)	0.048
Intraventricular hemorrhage	0.42	1.80	1.52 (0.83-2.79)	0.180

Figure 1. Flowchart of the study population. ICH, intracerebral hemorrhage; T1D, type 1 diabetes; T2D, type 2 diabetes.

Figure 2. Kaplan-Meier curves showing survival for (A) patients with and without diabetes (Log rank $P=0.021$), and (B) patients without diabetes, patients with type 1 diabetes (T1D), and type 2 diabetes (T2D) ($P=0.051$).

1013 consecutive
Helsinki ICH Study
patients

54 with prior ICH;
18 with missing data
on prior strokes

941 Helsinki ICH
Study patients with
first ICH

813 nondiabetic
patients

115 with T2D

13 with T1D

31 FinnDiane
study patients with
T1D and first ICH

3 patients died before
hospitalized

28 with T1D

Study population
(N=969):

813 nondiabetic
41 with T1D
115 with T2D

A **B**

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