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RESEARCH ARTICLE

Growth hormone and outcome in patients with intracerebral hemorrhage: a pilot study

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Abstract

Background: Endocrine alterations of the hypothalamic-pituitary-axis are one of the first measurable physiological changes in cerebral insults. During acute stress, human growth hormone (GH) is stimulated and has shown to have a prognostic value in various diseases. Within this pilot study, we evaluated the prognostic value of GH in patients with acute intracerebral hemorrhage (ICH).

Methods: In a prospective observational study in 40 consecutive patients with ICH, GH was measured on admission. The prognostic value of GH to predict 30-day mortality and 90-day functional outcome was assessed. Favorable functional outcome was defined as Barthel Index score >85 points and Modified Rankin Scale <3 points.

Results: GH levels were increased in patients who died within 30 days as compared to survivors (0.45 (IQR 0.20–1.51) vs. 1.51 (IQR 0.91–4.08) $p = 0.03$), and in patients with an unfavorable functional outcome as compared to patients with a favorable functional outcome after 90 days 0.28 (IQR 0.16–0.61) vs. 0.78 (IQR 0.31–1.99) $p = 0.03$). For mortality prediction, receiver-operating-characteristics revealed an area under the curve (AUC) on admission for GH of 0.78 (95% CI 0.60–0.96), which was in the range of the Glasgow Coma Score (GCS) (AUC 0.82 (95% CI 0.59–1.00) $p = 0.80$). For functional outcome prediction, GH had an AUC of 0.71 (95% CI 0.54–0.87), which was statistically not different from the GCS (AUC 0.81 (95% CI 0.68–0.94) $p = 0.36$).

Conclusions: In our small cohort of patients with acute ICH, elevated GH level were associated with increased mortality and worse outcome. If confirmed in a larger study, GH levels may be used as an additional prognostic factor in ICH patients. (ClincalTrials.gov number NCT00390962).

Keywords: growth hormone, intracerebral hemorrhage, mortality, outcome

Introduction

Changes in the hypothalamo-pituitary-adrenal axis are one of the first measurable physiological responses in cerebral insults (Olsson et al., 1992). A major surrogate of the host's response to stress is the activation of the anterior pituitary function, which leads to a continuum of neuroendocrine changes aimed to support the integrity of host deference (Van den Berghe, 2001, Vanhorebeek and Van den Berghe, 2006). Activation of the hypothalamic-pituitary axis in critical illness during the early phase leads to an augmentation in the release of growth hormone (GH), and to an increase in circulating levels (Ross et al., 1991). In this context, GH has been shown to have a prognostic value in various diseases. For example, GH plasma concentrations on admission are independent predictors for mortality in critically ill adult patients (Schuetz et al., 2009). An elevation of GH was also observed in patients with traumatic head injury and ischemic stroke, and was associated with poor outcome (Della Corte et al., 1998, Neidert et al., 2011). Whether

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GH levels also predict outcome in acute intracerebral hemorrhage (ICH) remains unclear.

Ten to twenty percent of all strokes are due to spontaneous acute intracerebral hemorrhage (ICH) and account for a high mortality and morbidity (Bamford et al., 1990). For an optimal care and allocation of healthcare resources, early risk assessment with estimate of the severity of disease and later prognosis is important. Glasgow Coma Score (GCS), hematoma volume and age, especially when used in combination, are known to be strong individual outcome predictors in hemorrhagic stroke patients (Hemphill et al., 2001, Broderick et al., 1993, Ruiz-Sandoval et al., 2007). Rapidly measurable biomarkers have gained interests regarding diagnosis (Laskowitz et al., 2009, Lynch et al., 2004, Foerch et al., 2009) and outcome prediction in ischemic and hemorrhagic stroke patients (Whiteley et al., 2008). The specific pathophysiological background of each biomarker thereby plays a subsidiary role: markers that allow to prognosticate outcome in patients with ICH may be a surrogate of e.g. neuroinflammatory response (MMP-9) (Alvarez-Sabin et al., 2004), direct brain damage and glial activation (S100B) (James et al., 2009) or general stress response (copeptin) (Zweifel et al., 2010). In the early hospital stage and in combination with clinical findings, biomarkers could thereby contribute to the prognostication and potentially to the decision making process and optimizing the subsequent management in patients with ICH. We hypothesized that elevated circulating GH levels are associated with adverse outcome in patients with acute ICH and tested this hypothesis in a pilot study.

Patients and methods

Study design and setting

This is a prospective cohort study conducted at the University Hospital Basel, Switzerland (Clinical Trials.gov number, NCT00390962). From November 2006 until November 2007, 605 consecutive patients with presumed stroke were admitted to the emergency department with symptom onset within 72 hours. Of the total, 362 had an ischemic stroke, 40 had a acute hemorrhagic stroke and 203 patients had a transient ischemic attack or another diagnosis. For the purpose of this paper, only patients with spontaneous ICH were analyzed. Patients with a subarachnoid hemorrhage or traumatic ICH were not considered for analysis. Informed consent was obtained from the patient or relatives, respectively.

Neuroimaging

The *ABC/2* method was used to assess the ICH volume on the initial CT scan (Kothari et al., 1996). *A* is the greatest diameter on the largest hemorrhage slice, *B* is the diameter perpendicular to *A*, and *C* is the number of axial slices with hemorrhage multiplied by the slice thickness.

Clinical variables and follow up

On admission within 72 hours from symptom onset, severity of disease was assessed with the GCS and relevant comorbidities were assessed by the Charlson comorbidity index (Goldstein et al., 2004, Gill et al., 2004). Interviews were performed by trained medical students, blinded to GH values for the assessment of 30-day mortality and functional outcome after 90 days. To assess functional outcome, patients were classified according to the Barthel index (BI) (Mahoney and Barthel, 1965) and modified Rankin Scale (mRS) (RANKIN, 1957). The primary endpoint of this study was mortality within 30 days from hospitalization. The secondary endpoint was functional outcome after 90 days. Thereby, favorable outcome was defined as BI>85 and mRS<3.

Assays

Results of the routine blood analyses including C-reactive protein (CRP) (mg/ml), glucose (mmol/l) and white blood cells (WBCs) (counts) were recorded in all patients. Plasma was collected on admission simultaneously with the first routine blood sampling in plastic tubes containing ethylenediaminetatraacetic acid (EDTA) in the emergency room. They were placed on ice and then centrifuged at 3000*g*, and plasma was frozen at–70 °C until batch-assayed. Serum GH (ng/ml) was measured using a newly developed, highly specific human GH immunoassay with a functional assay sensitivity of 0.027 ng/ml (Bidlingmaier et al., 2009).

Statistical analysis

Discrete variables are expressed as counts (percentage), and continuous variables as medians and interquartile ranges (IQR), unless stated otherwise. Mann–Whitney U test was performed for two-group comparison and the Kruskal–Wallis one-way analysis of variance was used if more than two groups were being compared. Univariate regression models were calculated to evaluate the prognostic accuracy of GH levels and other prognostic parameters. Thereby, logarithmic transformation was performed to obtain normal distribution for skewed variables (i.e. GH). We did not perform multivariate analysis due to the limited number of outcomes and risk of overfitting. Receiver-operating-characteristics (ROC) were calculated with the area under the curve (AUC) as an overall discriminatory measure. *p*-Values less than 0.05 were considered to indicate statistical significance. All calculations were performed using STATA 11.0 (Stata Corp, College Station, TX).

Results

Patient population

Eighteen of the 40 patients were female (45%) with median age of 71 years (IQR 64–78 years). The median GCS on admission was 14 (IQR 13–15). The hematoma was located in mostly in the basal ganglia or lobar, and median hematoma volume was 17.8 ml (IQR 6.3–36.3).

Table 1. Baseline characteristics of ICH cohort ($n=40$).

	Survivors ($n=34$)	Non-survivors ($n=6$)	p
Demographics			
Age (years)	69.5 (61.5–75.8)	80 (73.3–82.3)	0.06
Gender (female)	38% (13)	80% (5)	0.04
Clinical parameters			
GCS*	15 (14–15)	10 (4–13)	0.009
Charlson index	1 (0–1)	1.5 (1–2)	0.18
Body temperature (C°)	37.1 (36.7–37.4)	36.0 (35.9–37.5)	0.32
Hematoma volume in ml	13 (5–30)	69 (60–75)	0.003
ICH score†	1 (0–1)	3 (2.5–4)	0.002
Hypertension	67.7% (23)	100% (6)	0.444
Drugs (antiplatelets, anticoagulants)	26.5% (9)	0	NA§
Location			
Basal ganglia	44.1% (15)	50% (3)	0.75
Lobar	47.1% (16)	50% (3)	0.72
Infratentorial	8.8% (3)	0	NA§
Presence of IVH†	20.6% (7)	33.3% (2)	0.602
Laboratory values			
Glucose (mmol/l)	6.6 (5.8–7.8)	7.7 (6.1–8.4)	0.64
White blood cells (counts)	9.5 (6.7–11.6)	8.7 (7.5–8.8)	0.58
C-reactive protein (mg/l)	6 (3–18)	12 (3–81)	0.54
GH level (ng/ml)	0.45 (0.20–1.51)	1.51 (0.91–4.08)	0.03

Values are presented as median (lower quartile, upper quartile) or % (counts).
*GCS = Glasgow Coma Scale; §NA = not available; †ICH score according to Hemphill et al. 2001.

Seven patients received either an intraventricular drain or underwent hematoma evacuation. The presence of an AVM or cerebral aneurysm was angiographically excluded in all patients. Additional baseline characteristics are presented in Table 1.

The median GH value on admission was 0.58 ng/ml (IQR 0.23–1.64). The median time from symptom onset to blood withdrawal for GH determination was 13 hours, (IQR 5–32.5) with the following distribution: 7 patients (0–3 hours), 6 patients (3–6 hours), 7 (6–12 hours), 9 patients (12–24 hours) and 11 (24–72 hours). There was no significant difference of GH levels between these groups. Also, there were no significant differences in GH levels in patients according to the location of ICH: GH in basalganglia ICH was 0.61 ng/ml (IQR 0.26–1.6), in lobar ICH was 0.43 ng/ml (IQR 0.21–0.94) and in infratentorial hemorrhages was 1.6 ng/ml (IQR 0.99–1.9) (Kruskal–Wallis $p=0.55$). GH levels on admission correlated with Charlson Index ($r=0.37$, $p=0.02$) whereas no significant association of GH and age, GCS, hematoma volume, white blood cells or CRP was found. The median GH level on day one was 0.35 ng/ml (IQR 0.16–0.59; $n=31$), on day three 0.27 (IQR 0.01–0.82; $n=22$) and on day five 0.36 ng/ml (IQR 0.21–1.14; $n=21$), without any significant differences between the 3 days in patients who had all three measurements (Kruskal–Wallis $p=0.70$).

Table 2. Prediction of 30 day mortality ($n=6$) in univariate analysis of all patients ($n=40$).

Parameter	Odds ratio	95% CI		p
Age	1.11	1.00	1.23	0.054
Gender	8.08	0.85	77.07	0.07
GCS	0.74	0.58	0.93	**0.01**
Charlson index	1.11	0.71	1.17	0.65
Body temperature	0.58	0.17	2.01	0.39
Hematoma volume	1.05	1.01	1.08	**0.006**
ICH score	3.92	1.49	10.23	**0.005**
Glucose	1.15	0.66	1.99	0.62
CRP	1.03	0.98	1.07	0.22
WBC	0.87	0.63	1.19	0.38
GH	8.80	1.19	64.96	**0.03**

Mortality

Six patients died within 30 days, thus mortality was 15%. Non-survivors tended to be older and were more frequently females. Three non-survivors had basalganglia hemorrhage and three had lobar hemorrhage. On admission, neurological examination revealed a lower GCS level in non-survivors as compared to survivors (10 (IQR 5–13) vs. 14 (IQR 14–15), $p=0.009$). GH levels in non-survivors were significantly increased as compared to levels in survivors (0.45 ng/ml (IQR 0.20–1.51) vs. 1.51 (IQR 0.91–4.08), $p=0.03$).

In univariate logistic regression analysis, only GCS (OR 0.74, 95% CI 0.58–0.93), the volume of ICH (OR 1.05, 95% CI 1.01–1.08), ICH Score (OR 3.92, 95% CI 1.49–10.23) and GH levels (OR 8.80, 95% CI 1.19–64.96) were significantly associated with mortality (Table 2). The overall discriminatory accuracy of GH for mortality as assessed in ROC curve analysis (AUC 0.78 (95% CI 0.59–0.97) was not significantly different from the GCS (AUC 0.82 (95% CI 0.59–1.00), $p=0.80$) and ICH Score (Hemphill et al., 2001) (AUC 0.89, (95% CI 0.76–1.00), $p=0.42$).

Functional outcome

Eighteen patients (45%) had a favorable outcome defined as BI ≥85 and mRS <3 points, and 22 patients (55%) had an unfavorable outcome on day 90. Unfavorable outcome was similar in the different ICH locations (56% in basalganglia hemorrhage, 53% in lobar hemorrhage and 67% in infratentorial hemorrhages, $p=0.9$). GH levels on admission were significantly higher in patients with unfavorable outcome (0.28 (IQR 0.16–0.61) vs. 0.78 (IQR 0.31–1.99), $p=0.03$). In univariate logistic regression analysis GCS, age, the volume of ICH, ICH Score and GH were significant predictors of functional outcome (Table 3). In ROC analysis, GH demonstrated an AUC of 0.71 (95% CI 0.54–0.87), which was not statistically different from lesion size (AUC 0.75 (95% CI 0.60–0.91), $p=0.66$), the GCS (AUC 0.81 (95% CI 0.68–0.94), $p=0.36$) and the ICH Score (AUC 0.83, (95% CI 0.71–0.95), $p=0.21$).

Table 3. Prediction of adverse 90 days outcome defined as a BI <85 points and mRS < 3 ($n = 22$) in univariate analysis of all patients ($n = 40$).

Parameter	Odds Ratio	95% CI		p
Age	1.09	1.01	1.16	***0.02***
Gender	2.40	0.66	8.72	*0.18*
GCS	0.42	0.19	0.94	***0.04***
Charlson index	1.88	0.96	3.68	*0.07*
Body temperature	0.54	0.21	1.39	*0.20*
Hematoma volume	1.06	1.01	1.10	***0.02***
ICH score	5.48	1.81	16.48	***0.002***
Glucose	0.99	0.66	1.51	*0.98*
CRP	1.04	0.98	1.10	*0.19*
WBC	1.03	0.86	1.24	*0.73*
GH	4.40	1.10	17.70	0.04

Discussion

In this prospective pilot study including 40 consecutive patients with ICH, we found 3-fold increased circulating GH levels in patients who subsequently died; GH serum levels on admission were significantly associated with 30-day mortality and tended to be associated with functional outcome after 90 days. GH levels in our study cohort were higher as compared to GH levels measured with the same immunoassay in a study in young and healthy volunteers (Bidlingmaier et al., 2009). Evidence supports the fact that GH increases acutely upon an individual stress level of patients and thus mirrors the stress associated with the severity and extent of illness (Van den Berghe, 2001, Vanhorebeek and Van den Berghe, 2006). Accordingly, GH has also been shown to have a prognostic value in other diseases: Non-surviving children with meningococcal sepsis had markedly higher GH levels as compared to survivors (de Groof et al., 2002). Another study in children with sepsis or septic shock found similar results (Onenli-Mungan et al., 2004). In critically ill adult patients, GH plasma concentrations on admission are independent predictors for mortality (Schuetz et al., 2009). The resulting increase of GH itself may have a deleterious effect, as critically ill patients treated with recombinant GH had an increase in mortality due to uncontrolled infections and development of multiple organ failure (Takala et al., 1999). Thereby, various pathophysiological explanations have been proposed to explain the excess in mortality observed after GH treatment failure (Takala et al., 1999).

Already in 1972, an association of increased GH secretion and the severity of ischemic and hemorrhagic stroke was described (Huff et al., 1972). In our study in patients with hemorrhagic stroke, we showed that the discriminative power of GH was within the range of GCS, hematoma volume, age and ICH Score (Hemphill et al., 2001). The finding in our present study validates and further extends the finding of this early study, as the clinical value of GH has never been interpreted as a potential prognostic marker in hemorrhagic stroke patients.

It has been reported that in patients with ischemic stroke there was a significant correlation between the NIHSS and GH on admission (Neidert et al., 2011). Furthermore, GH levels were higher in patients who died, than in those who survived. Although GH was associated with stroke severity, it failed to show to be an independent predictor (i.e. from other known risk factors in ischemic stroke) of functional outcome after 90 days and 1 year in ischemic stroke patients.

Studies on circulating GH levels have largely been conducted in the rehabilitation phase after ischemic stroke, subarachnoid hemorrhage or traumatic brain injury (Aimaretti et al., 2004, Bondanelli et al., 2006, Boehncke et al., 2011). These studies focused primarily on the pathophysiology of the pituitary dysfunction in a later phase after ictus, and its impact to outcome of such patients. Our present study indicates that acute increased circulating GH levels are associated with worse outcome in patients with ICH. Though not specific, this marker might be a candidate for risk stratification similar to inflammatory markers such as the FDA approved CRP for risk stratification in ischemic vascular diseases (Katan and Elkind, 2011).

Despite the strength of our prospective enrolment, our study has limitations. First, our cohort is too small to perform multivariate regression analysis to demonstrate that GH is an independent prognostic marker. With the exception of the Charlson Index, however, there were no significant associations of GH levels and other parameters measured simultaneously on admission. Second, the median GCS of 14 was higher and the median hematoma volume of 17.8 ml was lower compared to other studies. For example in the Hemphil study (Hemphill et al., 2001), the mean GCS was 10 ± 4 and hematoma was $27 \pm 27\,cm^3$. We suppose that this may reflect the immediate availability of CT scans to all patients admitted to our hospital, even those with minor symptoms as well as the fact that the studied cohort itself presented with relatively mild ICH. Third, our cohort included non-surgically and surgically treated patients. As the STICH trial did not show any significant benefit of early surgery vs. initial conservative treatment, (Mendelow et al., 2005) we believe that the type of treatment did not differentially influence prognosis. Fourth, we included a rather heterogeneous population as patients were recruited within 72 hours after onset of clinical symptoms. This mirrors clinical routine where patients arrive in different stages after symptom onset. Another study in critical ill patients has shown that GH levels 24 hours after admission and at discharge were not significantly different from the initial measurement (Schuetz et al., 2009). Fifth, we only measured GH levels once a day in the morning. As the GH secretion is pulsatile, a serial standardized measurement of GH in all patients over one day might have provided a higher prognostic accuracy to predict outcome. The same applies for GHRH stimulation test, which might have better assessed the responsiveness of the hypothalamic-pituitary axis. However, the new results of this pilot study should encourage and propagate

further investigation of the measurement of GH in the setting of acute hemorrhagic stroke.

Conclusion

To conclude, in our pilot study GH was associated with 30-day mortality and functional outcome after 90 days in patients with ICH. If confirmed in future larger studies, in combination with clinical parameters, GH may allow improved risk assessment and allocation of targeted therapies in ICH patients.

Declaration of interest

The study was supported by in-house grants of the Department of Endocrinology and Neurology of the University Hospital of Basel, Switzerland and by the research grant for young scientists of the University Hospital of Basel Switzerland (to MK). Further, this study was supported by a research grant from the Swiss National Foundation (PP00P3-123346 to MCC). A.E. was an employee of SphingoTec GmbH, the developer of the assay. No funding was obtained from commercial sources for this study.

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