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Predictors of outcome in hypoglycemic encephalopathy

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ABSTRACT

Aims: The aim of this study was to investigate factors predicting poor prognosis in patients with hypoglycemic encephalopathy.

Methods: We retrospectively analyzed data on 165 consecutive patients with hypoglycemic encephalopathy. We evaluated their outcome 1 week after hypoglycemia onset using the Glasgow outcome scale (GOS) and compared the clinical features of patients with good outcomes (GOS = 5) and poor outcomes (GOS ≤ 4).

Results: The poor-outcome group included 38 patients (23%). The initial blood glucose level in the poor-outcome group was lower than that in the good-outcome group ($p = 0.002$). The duration of hypoglycemia in the poor-outcome group was longer than that in the good-outcome group ($p < 0.001$). Body temperature during hypoglycemia in the poor-outcome group was higher than that in the good-outcome group ($p < 0.001$). Furthermore, lactic acid level in the poor-outcome group was lower than in the good-outcome group ($p = 0.032$). There was no significant difference in the frequency of posttreatment hyperglycemia between the good-outcome and poor-outcome groups ($p = 0.984$).

Conclusion: Profound and prolonged hypoglycemia, normal or higher body temperature, and a low lactic acid level during hypoglycemia may be predictors of a poor outcome in patients with hypoglycemic encephalopathy.

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1. Introduction

Hypoglycemic encephalopathy is caused by a lack of glucose availability to brain cells, and occurs as a consequence of a serious complication of insulin and/or oral hypoglycemic therapy, malnutrition, alcohol abuse, and insulinoma [12,17].

It may cause long-lasting coma, seizures, cognitive impairment, and other global and focal neurological deficits [14], and several studies have attempted to predict short-term [8,9,11,25] or long-term outcome [22], particularly by using MRI changes during the acute phase. In addition, the relationship between the MR imaging features and 1-week outcomes in patients with hypoglycemic encephalopathy has been

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evaluated prospectively [8]. Possible outcome predictors may include initial blood glucose level or duration of hypoglycemia [3], as demonstrated in animal studies (reviewed in Ref. [4]). In addition, several studies using rodent models have shown that a decrease in body temperature during hypoglycemia [2,18] or administration of lactic acid [23], an alternative neuronal energy substrate that can effectively bypass glycolysis [24], exerts protective effects against the development of hypoglycemia-induced neuronal injury. Other studies have also shown that posttreatment hyperglycemia might exacerbate neuronal damage, because hypoglycemic neuronal damage is not simply a result of energy failure resulting from lack of glucose, but is the result of a cell death program that is initiated by the re-introduction of glucose after a period of hyperglycemia referred to as glucose reperfusion injury [1,13,20].

We therefore retrospectively analyzed data on patients with hypoglycemic encephalopathy to test the following hypotheses: (i) profound and prolonged hypoglycemia is a poor prognostic factor, (ii) normal or higher body temperature is a poor prognostic factor, (iii) a low lactic acid level is a poor prognostic factor, and (iv) posttreatment hyperglycemia is a poor prognostic factor.

2. Subjects, materials and methods

Ethics approval was provided by Ethics Committees of participating hospitals. We performed a multicenter retrospective study on patients with hypoglycemic encephalopathy, who were admitted to our hospitals between 2005 and 2011. Hypoglycemic encephalopathy was defined as a state in which the patients had coma or stupor, with a blood glucose level of less than 50 mg/dL before glucose administration. Among the patients with hypoglycemic encephalopathy, we defined “hypoglycemic consciousness disturbance” as the state in which patients regain consciousness immediately after glucose administration in the emergency room. Patients with focal signs without consciousness disturbance and patients with consciousness disturbance due to any other cause were excluded.

In cases where the glucose levels were measured more than once, the initial blood glucose level was defined as the lowest blood glucose level recorded after admission to the hospital. The duration of hypoglycemia was defined as the time between onset of symptoms and the start of treatment. If the time of symptom onset was not available, the time last verified as having no symptoms was used. Axillary body temperatures on arrival were measured using electronic thermometers. Whole blood lactic acid on arrival was measured by an enzyme-electrode method. We evaluated the therapeutic outcome of the patients 1 week after the hypoglycemic episode by using the Glasgow Outcome Scale (GOS) [7] and compared the clinical features of patients with a good outcome (GOS = 5) with those of patients with a poor outcome (GOS \leq 4).

The data are presented as mean \pm standard deviation (SD) values or median and interquartile range. Statistical analyses were performed using the Fisher exact, Mann–Whitney rank sum or Student’s t-test when appropriate with $p < 0.05$ considered statistically significant.

3. Results

We examined the clinical characteristics of 165 consecutive patients with hypoglycemic encephalopathy (Table 1). Among these 165 patients, 19 (12%) patients exhibited hypoglycemic consciousness disturbance. One hundred twenty-three patients (75%) had past history of diabetes mellitus. The most frequent underlying causes of hypoglycemic encephalopathy were inappropriate medications (taking too much of certain hypoglycemic agents; 123 patients), gastrointestinal diseases (37 patients), and alcohol abuse (26 patients). Other causes include anorexia nervosa, acute adrenal insufficiency, dumping syndrome, and insulinoma. The good-outcome group included 127 patients (77%) and the poor-outcome group included 38 patients (23%), which included 11 patients with GOS 1 (death), 12 patients with GOS 2 (vegetative state), 6 patients with GOS 3 (severe disability), and 9 patients with GOS 4 (moderate disability). There were no autopsy cases.

Table 1 – A comparison of the clinical characteristics of patients in the good-outcome and poor-outcome groups. The number of patients includes overlapping causes of hypoglycemia (*). Normal lactic acid levels range from 0.5 to 1.6 mmol/L. Data are represented as mean \pm SD. The range is in parenthesis.

	All	Good outcome	Poor outcome	p value
Number of patients	165	127 [77%]	38 [23%]	
Causes of hypoglycemia*				
Medications	123	98	25	
Gastrointestinal diseases	37	25	12	
Alcohol abuse	26	19	7	
Other causes	13	11	2	
Age (years)	69.0 \pm 15.5 (25–94)	69.5 \pm 15.9 (25–94)	67.4 \pm 14.3 (33–94)	0.268
Sex (male:female)	91:74	67:60	24:14	0.260
Diabetes mellitus	123	98 [80%]	25 [20%]	0.106
Consciousness				
Coma	62 [38%]	35 [28%]	27 [71%]	
Stupor	103 [62%]	92 [72%]	11 [29%]	

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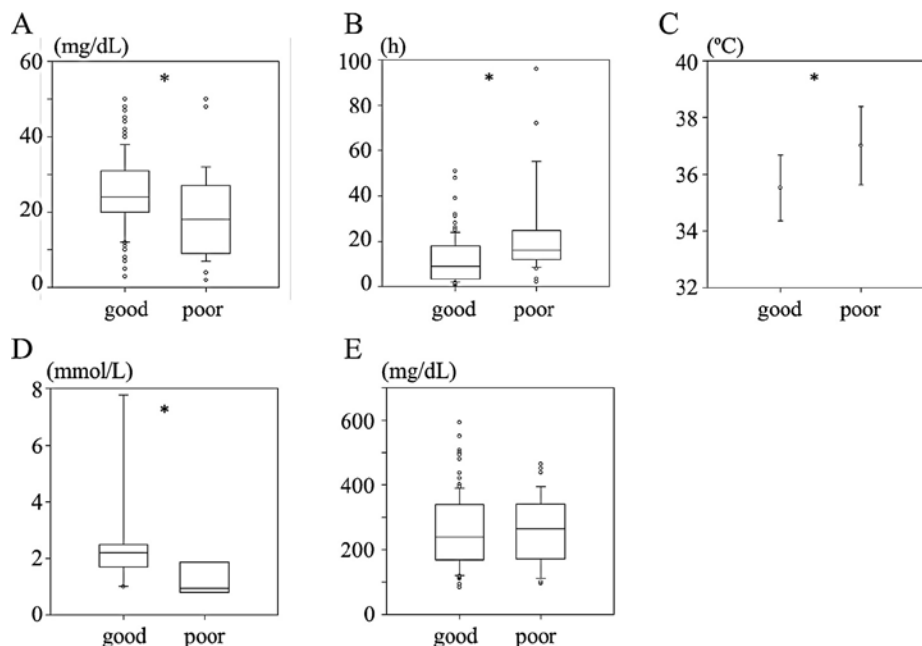


Fig. 1 – Comparison of clinical feature between good- and poor outcome groups. (A) Initial blood glucose level ($p = 0.002$; numbers of patients with good- and poor outcome are 116 and 33, respectively). (B) Duration of hypoglycemia ($p < 0.001$; numbers of patients with good- and poor outcome are 126 and 36, respectively). (C) Body temperature during hypoglycemia ($p < 0.001$; numbers of patients with good- and poor outcome are 127 and 38, respectively). (D) Lactic acid levels ($p = 0.032$; numbers of patients with good- and poor outcome are 11 and 8, respectively). (E) Highest blood glucose level after glucose administration ($p = 0.984$; numbers of patients with good- and poor outcome are 125 and 38, respectively). * $p < 0.05$.

There were no significant differences in age, sex, frequency of diabetes mellitus, and underlying cause of hypoglycemic encephalopathy between two groups (Table 1). The initial blood glucose level in the poor-outcome group was lower than that in the good-outcome group (18.0; 9.0–27.0 mg/dL vs 24.0; 20.0–31.0 mg/dL; median; interquartile range, respectively, $p = 0.002$; Fig. 1A). The duration of hypoglycemia in the poor-outcome group was longer than that in the good-outcome group (16.0; 12.0–24.8 h vs 9.0; 3.5–18.0 h; median; interquartile range, respectively, $p < 0.001$; Fig. 1B).

Body temperature during hypoglycemia in the poor-outcome group was higher than that in the good-outcome group (37.0 ± 1.4 °C and 35.5 ± 1.2 °C, respectively; $p < 0.001$; Fig. 1C). Hypothermia of less than 35 °C was frequently observed in the good-outcome group than in the poor-outcome group (35/127; 27.6% vs 3/38; 7.9%, $p = 0.012$). Hypothermia of less than 34 °C was observed only in the good-outcome group (14/127; 11.0% vs 0/38; 0%, $p = 0.041$).

The whole blood lactic acid level in the poor-outcome group was lower than that in the good-outcome group (1.0; 0.8–1.9 mmol/L vs 2.2; 1.7–2.5 mmol/L; median; interquartile range, respectively; $p = 0.032$; Fig. 1D), although the lactic acid level was only measured in 11 poor-outcome patients and 8 good-outcome patients. The median lactic acid level in the good-outcome group was elevated above the normal range (0.5–1.6 mmol/L).

The highest blood glucose level after glucose administration was high in both groups, and there was no significant difference in the blood glucose level after treatment between the 2 groups (265.5; 172.3–341.8 mg/dL vs 240.0;

169.5–341.0 mg/dL; median; interquartile range, respectively; $p = 0.984$; Fig. 1E). There was no significant difference in the frequency of posttreatment hyperglycemia of more than 200 mg/dl between the good-outcome and poor-outcome groups (78/127; 61.4% vs 24/38; 66%, $p = 0.846$). In addition, there was no significant difference in the frequency of posttreatment hyperglycemia of more than 300 mg/dl between the good-outcome and poor-outcome groups (41/127; 32.3% vs 13/38; 34.2%, $p = 0.824$).

Information was available on the precise time of symptom onset in 47 of 165 patients (28.5%). Among these 47 patients, 42 patients (89.4%) were present in the good-outcome group, whereas 5 patients (10.6%) were present in the poor-outcome group. Due to the small number of patients in the poor-outcome group, we were unable to statistically analyze the differences between the groups (Table 2).

4. Discussion

We demonstrated several novel findings regarding predictors of outcome in patients with hypoglycemic encephalopathy. First, we showed that profound and prolonged hypoglycemia may be a poor prognostic factor. It follows that a lower blood glucose level and longer duration of hypoglycemia can cause more severe hypoglycemic neuronal damage, thus resulting in a poor prognosis. However, a recent study demonstrated that initial clinical presentation including blood glucose level and duration of hypoglycemia were not correlated with the clinical outcome [22], although the number of patients was small

Table 2 – A comparison of the clinical characteristics of patients who were identified the precise time of symptom onset in the good-outcome and poor-outcome groups. The number of patients includes overlapping causes of hypoglycemia (*). Data are represented as mean \pm SD. The range or number of patients is in parenthesis.

	All	Good outcome	Poor outcome	p value
Number of patients	47	42 [89%]	5 [11%]	
Causes of hypoglycemia*				
Medications	36	33	3	
Gastrointestinal diseases	13	11	2	
Alcohol abuse	3	3	0	
Other causes	8	8	0	
Age (years)	68.5 \pm 12.9 (35–90)	68.2 \pm 13.4 (35–90)	71.2 \pm 8.2 (61–81)	0.268
Sex (male:female)	26:21	22:20	4:1	0.260
Diabetes mellitus	36	33 [92%]	3 [8%]	0.789
Initial blood glucose	27.2 \pm 11.4	27.8 \pm 11.5 (n = 41)	18.0 \pm 3.5 (n = 3)	0.153
Duration of hypoglycemia	4.7 \pm 5.0	4.3 \pm 4.2 (n = 42)	9.4 \pm 10.1 (n = 4)	0.224
Body temperature	35.3 \pm 1.0	35.3 \pm 1.0 (n = 41)	35.9 \pm 1.1 (n = 5)	0.120
Lactic acid	4.1 \pm 4.9	2.1 \pm 0.3 (n = 4)	7.8 \pm 8.6 (n = 2)	0.800
Highest blood glucose level	271.1 \pm 128.5	275.6 \pm 131.8 (n = 41)	234.2 \pm 99.8 (n = 5)	0.596

(13 patients). The inconsistency of the results may be caused by the difference in the definition of hypoglycemic coma between the 2 studies, because the previous study was confined to patients in a persistent coma or stupor for at least 24 h after the normalization of blood glucose.

Second, we demonstrated that normal or higher body temperature during hypoglycemia may be a poor prognostic factor in humans, as is the case with a rodent model that indicates that neuronal injury after hypoglycemia is temperature-dependent [18]. A recent study demonstrated that hypothermia is a frequent sign of severe hypoglycemia in patients with diabetes, indicating that hypothermia may represent an important compensatory mechanism in severe hypoglycemia, reflecting a decrease in energy demand during glucose deprivation [21]. In addition, it is possible that higher body temperature is associated with poorer outcomes in hypoglycemic encephalopathy in a similar manner to stroke [6,10]. Future studies are needed to determine if therapeutic hypothermia may improve the prognosis of patients with hypoglycemic encephalopathy.

Third, we demonstrated that a low lactic acid level during hypoglycemia may be a poor prognostic factor. A previous study has shown that infusion of lactic acid during hypoglycemia exerts protective effects on brain dysfunction in healthy humans [13]. In addition, a recent study using a rodent model demonstrated that lactate administration, when infused as an adjuvant to glucose after hypoglycemia, prevented acute or severe hypoglycemia-induced neuronal death [23]. These neuroprotective effects of lactic acid are explained by the findings that lactic acid is produced by astrocytes [15] and is metabolized as an important alternative neuronal energy substrate [16,24]. Our findings may be in line with these studies showing the neuroprotective effects of lactic acid against hypoglycemia, although further evaluation in larger series is needed.

Finally, we showed that hyperglycemia can occur frequently after treatment, although the highest blood glucose levels were not different between the good-outcome and poor-outcome groups. Several animal studies suggest that blood glucose levels should be raised cautiously with avoidance of hyperglycemia [5,19,20], while the present study demonstrated that posttreatment hy-

perglycemia caused by excessive glucose administration was frequently observed in the clinical setting, probably because it is difficult to determine optimal glucose dose especially in patients with diabetes. Because a rodent model demonstrated that the reintroduction of glucose after a sustained period of glucose deprivation may cause oxidative stress-mediated neuronal death [20], future studies need to determine whether posttreatment hyperglycemia could cause oxidative stress in human brains.

This study has some limitations. First, as this study had a retrospective design and because individuals accompanying the patient frequently provided insufficient information, it was difficult to determine the precise time of symptom onset. Therefore, the results of the analyses of this retrospectively collected data should be carefully interpreted. Second, we could not investigate the effect of air temperature of the place where the patients were found on body temperature of patients with hypoglycemic encephalopathy. Third, we did not investigate whether past history of recurrent hypoglycemia could affect the prognosis of patients with hypoglycemic encephalopathy.

In conclusion, profound and prolonged hypoglycemia, normal or higher body temperature, and a low lactic acid level during hypoglycemia may be predictors of poor outcome in patients with hypoglycemic encephalopathy. The present study provides fundamental information to help develop novel therapeutic approaches for patients with hypoglycemic encephalopathy, including therapeutic hypothermia, the administration of lactic acid, or antioxidants.

Conflict of interest

The authors declare that they have no conflict of interest.

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