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Seizure occurrences among hypoglycemic patients in the emergency department

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Abstract

Aim: Symptomatic hypoglycemia is a common problem in the emergency department (ED). However, without appropriate recognition and management, hypoglycemia remains a potentially fatal condition. The cause of sudden death associated with hypoglycemia might be attributed to cardiac arrhythmias and hypoxia with seizures. Despite advances in diabetes mellitus management and social background, the frequency and characteristics of patients with hypoglycemia-related seizures have remained unknown. Hence, our study aimed to investigate the frequency and characteristics of patients with hypoglycemia presenting with seizures in the ED.

Methods: This retrospective observational study was conducted in a single tertiary care center. Patient information was retrieved from the final diagnostic records in the ED. We reviewed all medical records and included patients with symptomatic hypoglycemia aged 16 years or older. The primary outcome was the frequency of seizures in patients with hypoglycemia. We also compared the initial blood sugar levels of the patients with and without seizures.

Results: We included a total of 380 patients (median age, 72 years, IQR 64–80 years; median initial blood sugar, 34 mg/dL, IQR 24–46; 62.9% male). Nineteen of 380 patients (5.0%) had seizures. Although 16 of the 19 patients had diabetes mellitus, none of the 19 patients had a history of epilepsy. The initial blood sugar levels of the patients with and without seizures were not significantly different ($p = 0.97$).

Conclusion: Approximately 5% of the patients with hypoglycemia presented with seizures. Blood glucose levels of hypoglycemic patients with and without seizures did not differ.

KEYWORDS
diabetes mellitus, hypoglycemia, insulin, paramedics, seizures

INTRODUCTION

Symptomatic hypoglycemia is a common problem in the emergency department (ED).[1] In Japan, the number of the patients with severe hypoglycemia transported to the ED is estimated to be 20,000 individuals per year.[2] The management of diabetes mellitus has changed to a more individualized and tailored approach, resulting in the decrease in the number of hypoglycemia cases and admissions.[3,4] However, without appropriate recognition and management, hypoglycemia remains a potentially fatal condition. For example, Gagnum et al. reported that hypoglycemia accounted for approximately 8% of mortality rate in patients with type 1 diabetes mellitus.[5] The cause of sudden death associated with hypoglycemia might be attributed to cardiac arrhythmias and hypoxia with seizures.[6,7] Although the mechanism

of seizures in hypoglycemia is not completely understood, hypoglycemia presumably induces neurotransmitter imbalance, resulting in neurotoxicity.[8,9]

In Japan, paramedics are not allowed to administer benzodiazepines to patients with seizures in prehospital settings. However, since 2014, the measurement of blood sugar and treatment with intravenous administration of glucose by paramedics in patients with hypoglycemia have been permitted. Thus, not only the physicians but also paramedics can provide treatment for patients experiencing seizures attributed to hypoglycemia, considering early recognition of the condition. Nevertheless, seizures caused by hypoglycemia are relatively uncommon and pose a risk of misdiagnosis of epilepsy.[8] To mitigate the risk of misdiagnosis, understanding the frequency and characteristics of seizures with hypoglycemia is crucial. Despite advances in diabetes mellitus management and social background, the frequency and characteristics of patients with hypoglycemia-related seizures have remained unknown for many years.[10] Hence, our study aimed to investigate the frequency and characteristics of patients with hypoglycemia presenting with seizures in the ED.

METHODS

Study design

This study was a retrospective observational study in a single tertiary care center. The study period was from January 2017 to December 2021.

Setting

Kurashiki Central Hospital is a 1172-bed tertiary care center in Western Japan. The emergency department of Kurashiki Central Hospital manages approximately 60,000 patients annually, including approximately 10,000 patients transported by ambulance or helicopter. We recorded the final diagnoses of the patients at discharge from the ED from electronic medical records.

Participants

Patients who experienced seizures due to hypoglycemia in our ED were diagnosed with "hypoglycemia," and this diagnosis was recorded as the final diagnosis, regardless of whether they had a seizure or not. Consequently, we retrieved information about patients diagnosed with "hypoglycemia" from our ED's final diagnosis records. We reviewed all medical records and included patients with symptomatic hypoglycemia aged 16 years or older. While a precise definition for blood glucose levels signifying hypoglycemia is not available, clinical understanding commonly identifies blood glucose levels below 70 mg/dL as inducing various symptoms associated with hypoglycemia.[11] Cases were included in the study where even if the patient's initial blood sugar level in the ED was higher than 70 mg/dL, the symptoms were still considered hypoglycemia and improved by administering glucose by patients themselves or paramedics. We excluded patients whose symptoms and diagnoses were not considered hypoglycemia (e.g., stroke, meningitis, or epilepsy).

Variables

We reviewed all medical records and extracted patient data regarding age, sex, vital signs, initial blood sugar level, symptoms, presence of diabetes mellitus, insulin use, comorbidities, treatment (glucose, glucagon, vitamin B1, naloxone, and diazepam), hospital admission, and death in the hospital. In Japan, paramedics are allowed to measure the blood sugar of patients whose Japan Coma Scale score is 10 or higher, and if the blood sugar is low, they can administer glucose to the patients under the direction of the local medical control system. Therefore, we reviewed the medical records of paramedics and extracted data on the vital signs, symptoms, and initial blood sugar levels of patients who had been treated by paramedics.

Measurement

The primary outcome was the frequency and characteristics of seizures in patients with hypoglycemia. We also compared the initial blood sugar levels of the patients with and without seizures.

Statistical method

As the continuous variables were expected to be non-normally distributed, the results are reported as the median and interquartile range (IQR). Variables with continuous outcomes (e.g., initial blood sugar levels) were evaluated using the non-parametric Mann–Whitney U-test. Variables with dichotomous outcomes (e.g., sex) were evaluated using Fisher's exact test. Statistical analyses were performed using EZR version 1.37.[12]

RESULTS

Characteristics of the study participants

A total of 441 patients were diagnosed with hypoglycemia in the ED during the study period. Upon reviewing their medical records, we excluded 33 patients younger than 16 years and 28 patients whose diagnoses were not considered symptomatic hypoglycemia. The remaining 380 patients were included (median age 72 years, IQR 64–80 years; median initial blood sugar 34 mg/dL, IQR 24–46; 62.9% male) (Figure 1).

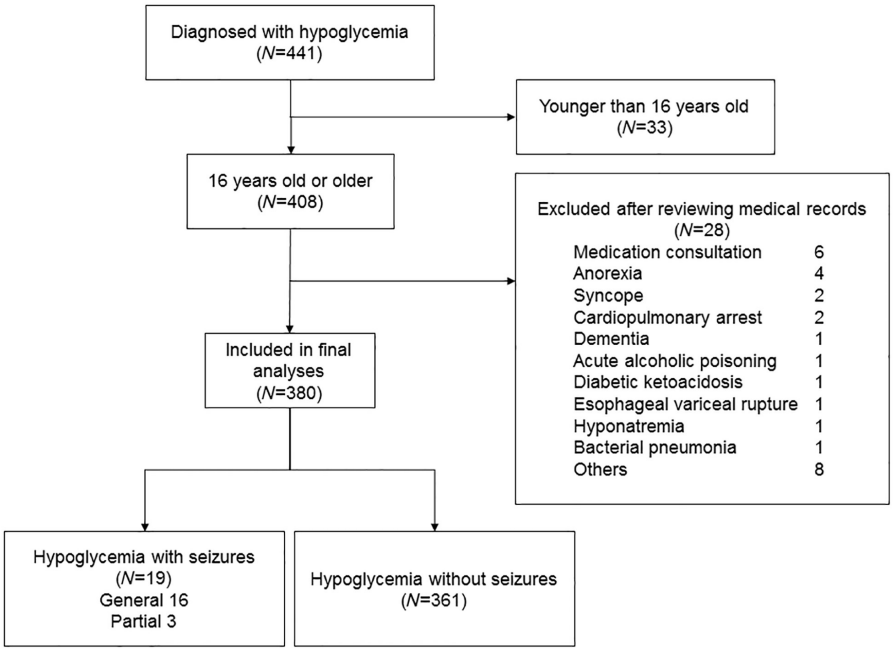

FIGURE 1 Selection of study participants. A total of 441 patients were initially diagnosed with hypoglycemia in the emergency department. After excluding 33 patients, 380 patients (19 with seizures and 361 without seizures) were included in the study.

Participants' characteristics are presented in Table 1. Among the 380 patients with hypoglycemia, 19 patients (12 men and seven women) experienced seizures while the remaining 361 patients (227 men and 134 women) did not experience seizures. The vital signs of the patients with and without seizures were similar and mostly normal, except for slight hypertension and altered level of consciousness. The Glasgow Coma Scale was 10 (IQR; 7–14) in the patients with seizures and 12 (IQR; 7–14) in the patients without seizures, respectively. Among all patients with hypoglycemia, the number of patients treated by paramedics was 59. Type 2 diabetes mellitus was the most frequent underlying disease, followed by type 1 diabetes mellitus and others. Other than diabetes mellitus, alcohol-related diseases were the most frequent cause of hypoglycemia. The median initial blood sugar is 34 mg/dL in both patients with and without seizures, respectively. Ten of the 19 patients with seizures and 182 of the 361 patients without seizures were admitted to the hospital.

Main results

In total, 19 of 380 patients (5.0%) had seizures. We show the clinical characteristics of patients with symptomatic hypoglycemia presenting with seizures in Table 2. Of the 19 patients with seizures, 16 had general seizures and three had partial seizures. The underlying diseases of the patients with seizures were type 2 diabetes mellitus in eight patients, type 1 diabetes mellitus in eight patients, alcohol-related disease in two patients, and post-gastrectomy syndrome in one patient. Of the 16 patients with diabetes mellitus, six of eight patients with type 2 diabetes mellitus patients and all 8 type 1 diabetes mellitus patients used insulin. Three patients were treated by paramedics. Glucose was administered intravenously to 18 of the 19 patients while the remaining one patient ingested glucose orally. Vitamin B1 was administered in four patients, and diazepam was administered in three patients. None of the patients were administered glucagon. Seizures in 16 of 19 patients were controlled by the administration of glucose. The seizures in the remaining three patients were controlled by the administration of diazepam before the administration of glucose (Table S1). One patient in the non-seizure group was administered diazepam for alcohol withdrawal symptoms. Although 10 out of the 19 patients with seizures were admitted to the hospital, none died. The initial blood sugar levels of the patients who had seizures and those without seizures were not significantly different ($p = 0.97$).

DISCUSSION

In our study, the frequency of seizures with hypoglycemia in the ED was 5% (19/380). There was no difference in blood sugar levels between patients with and without seizures.

A previous study that investigated the cause of hypoglycemia or neurological symptoms in the ED reported that the frequency of seizures due to hypoglycemia was 7% (9/125).[10] This frequency was not different from that observed in the current study (19/380, $p = 0.37$). Three patients with seizures in a previous study had a medical history of epilepsy and six patients had alcohol-related seizures.[10] In our study, none of the patients had a medical history of epilepsy and two patients had alcohol-related disease without a history of seizures. We were also unable to identify organic brain disease or history of epilepsy in patients with partial seizures upon

TABLE 1 Characteristics of study participants.

	All	Seizure	Without seizure
Number (Man/Woman)	380 (239/141)	19 (12/7)	361 (227/134)
Age (IQR)	72 (64–80)	67 (48–74)	72 (64–80)
Initial vital signs			
Systolic blood pressure (IQR)	152 (130–174)	168 (147–208)	152 (129–173)
Diastolic blood pressure (IQR)	76 (63–89)	87 (78–93)	75 (63–88)
Heart rate (IQR)	80 (70–92)	83 (75–98)	80 (69–91)
Respiratory rate (IQR)	18 (16–20)	18 (16–23)	18 (16–20)
Body temperature (IQR)	36 (35.5–36.4)	36.3 (36.1–36.7)	36.0 (35.4–36.4)
Glasgow Coma Scale (IQR)	12 (7–14)	10 (7–14)	12 (7–14)
Underlying disease			
Type 1 diabetes mellitus (%)	91 (24.0)	8 (42.1)	83 (23.0)
Type 2 diabetes mellitus (%)	204 (53.7)	8 (42.1)	196 (54.3)
Alcohol-related diseases (%)	57 (15.0)	2 (10.5)	55 (15.2)
Presentation and treatment			
Unconsciousness (%)	289 (76.1)	16 (84.2)	273 (74.0)
Hemiparesis (%)	9 (2.4)	0 (0)	9 (2.4)
Any seizure (%)	19 (5.0)	19 (100)	0 (0)
General seizure (%)	16 (4.2)	16 (84.2)	0 (0)
Partial seizure (%)	3 (0.8)	3 (15.8)	0 (0)
Initial blood sugar (IQR)	34 (24–46)	34 (23–46)	34 (24–45)
Intravenous (%)	353 (92.9)	18 (94.7)	335 (90.8)
Oral (%)	27 (7.1)	1 (5.3)	26 (7.0)
Glucagon (%)	0 (0)	0 (0)	0 (0)
Vitamin B1 (%)	86 (22.6)	4 (21.1)	82 (22.2)
Diazepam (%)	4 (1.1)	3 (15.8)	1 (0.3)
Admission (%)	192 (50.5)	10 (52.6)	182 (49.3)
Death after admission (%)	8 (2.1)	0 (0)	8 (2.2)

Abbreviation: IQR, interquartile range.

reviewing their medical records. Our study results suggest that a medical history of epilepsy may not be strongly related to the occurrence of seizures in patients with hypoglycemia. Another study that investigated patients with type 1 diabetes mellitus showed that the frequency of seizures due to hypoglycemia was 2.2% (5/229).[13] The frequency of seizures due to hypoglycemia in patients with type 1 diabetes mellitus in our study was 8.8% (8/91, $p = 0.01$). One reason for this difference is that elderly patients manage their medication or physical condition less than younger patients. The age of the patients with type 1 diabetes mellitus with seizures in our study was higher (60 years old; IQR 47–73) than that in the previous study (37 years old; IQR 34–42).[13]

The symptoms of hypoglycemia are nonspecific and classified as neurogenic or neuroglycopenic. Neurogenic symptoms, such as tremulousness, palpitations, anxiety, sweating, hunger, and paresthesia, are caused by autonomic nervous system reactions. In contrast, neuroglycopenic symptoms, such as confusion, warm sensation, weakness or fatigue, severe cognitive failure, seizures, and coma, are caused by glucose deprivation in the brain.[14] Hypoglycemia affects the hippocampus and amygdala and it induces epileptical discharge in animal models.[15] One of the hypotheses in humans is that acute hypoglycemia affects high metabolic-demand brain sites, such as the mesial temporal lobe and the peri-rolandic cortex, and it triggers motor presentations of seizures.[16] Although the appearance of hypoglycemic symptoms also depends on the glucose concentration, the threshold for glucose levels associated with seizures is unclear.[15] Our current study showed no difference in the initial glucose levels between patients with and without seizures.

In our study, 59 of the 380 patients were treated for hypoglycemia by paramedics. Although all patients with seizures were brought in by paramedics, only three patients had their blood sugar measured and were administered glucose by them. Generally, the rate of hypoglycemia in patients with seizures is very low, and measuring blood sugar is associated with a delay in administering benzodiazepines in prehospital situations.[17] Although administration of benzodiazepines to patients with active seizures is crucial, benzodiazepine

TABLE 2 Clinical characteristics of patients with symptomatic hypoglycemia presenting with seizures.

Age	Sex	Blood sugar (mg/dL)	Type of seizures	Treated by paramedics	Possible cause	Insulin usage	Administration route of glucose	Diazepam	Co-morbidity	Admission	Outcome
21	M	34	General	–	DM1	+	Intravenous	+	Depression	+	Recovered
27	F	20	General	+	DM1	+	Intravenous	–	Hyperthyroidism	–	Recovered
28	F	42	General	+	DM1	+	Intravenous	–	Pregnancy	+	Recovered
47	F	48	General	–	DM1	+	Intravenous	–		–	Recovered
47	M	51	Partial	+	DM1	+	Intravenous	–		–	Recovered
64	M	43	General	–	DM1	+	Intravenous	–	Hypertension	–	Recovered
78	M	25	General	–	DM1	+	Intravenous	–		–	Recovered
79	M	19	General	–	DM1	+	Intravenous	–	Bronchial asthma, Dilated cardiomyopathy	+	Recovered
49	F	30	Partial	–	DM2	+	Oral	–		–	Recovered
67	M	15	General	–	DM2	–	Intravenous	–	Urinary tract infection	+	Recovered
70	M	53	General	–	DM2	+	Intravenous	–		–	Recovered
70	M	29	General	–	DM2	–	Intravenous	–	Nephropathy	+	Recovered
71	F	43	General	–	DM2	–	Intravenous	+	Infectious enteritis	+	Recovered
76	M	22	General	–	DM2	+	Intravenous	–		+	Recovered
77	M	55	Partial	–	DM2	+	Intravenous	–		+	Recovered
83	F	24	General	–	DM2	+	Intravenous	–	Chronic heart failure, Nephropathy, Hypertension	–	Recovered
51	F	40	General	–	Alcohol-related	–	Intravenous	–		+	Recovered
72	M	21	General	–	Alcohol-related	–	Intravenous	+	Chronic obstructive pulmonary disease	+	Recovered
61	M	66	General	–	Post-gastrectomy	–	Intravenous	–		–	Recovered

Abbreviations: DM1, type 1 diabetes mellitus; DM2, type 2 diabetes mellitus.

administration by paramedics is not permitted in Japan. In our study, seizures in 16 of 19 patients were arrested by glucose administration. Although the remaining three patients were administered benzodiazepine before being diagnosed with hypoglycemia, earlier diagnosis would have prompted glucose administration. Thus, blood sugar level measurement and glucose administration in patients with seizures by paramedics in such situations in Japan are practical. However, in prehospital situations, paramedics must prioritize maintaining the airway and consistent breathing. Consequently, assessing blood glucose levels becomes challenging in such circumstances. Although they can consider investigating blood glucose levels, especially in patients with distinctive medical histories, such as the presence of diabetes mellitus or alcohol-related diseases, maintaining the airway, breathing, and circulation is the primary concern.

Limitations

Our study has some limitations. First, because our study was a retrospective review, diagnosis and treatment were left to the treating physicians or paramedics. Although we carefully reviewed all medical records, detailed convulsion forms and durations were unknown for some patients.

Second, the methods and timings for measuring blood glucose levels varied among patients, paramedics, and physicians. Some patients measured their glucose levels at home, whereas others had their glucose levels measured by paramedics in ambulances. Although our study was retrospective in design, prospective studies might find it challenging to standardize the timings and methods of measuring blood glucose owing to the diverse situations in which patients may undergo or medical staff may need to conduct these measurements during emergencies. Consequently, the blood glucose levels in our study's results may offer feasibility in clinical settings.

Third, our study exhibited selection bias. Our emergency department accepts the largest volume of patients with mild-to-severe conditions in the medical bloc region. Nonetheless, it is important to acknowledge that some patients experiencing hypoglycemia might have been treated or transferred to other hospitals within the same region. A multicenter study involving hospitals within this region should be conducted to ascertain the frequency of seizures in patients with hypoglycemia within the general population.

In our study, none of the patients with hypoglycemia used glucagon. Thus, whether glucagon is effective in stopping seizures in patients with hypoglycemia remains unknown. Patients in Japan use glucagon less frequently.[18] Since its approval in 2020, the use of nasal glucagon has increased. We hope to conduct future studies in other regions to clarify the effectiveness of glucagon in treating seizures in patients with hypoglycemia. We only clarified the prevalence of seizure with hypoglycemia in the patients with hypoglycemia owing to the limitation concerning the retrospective design and final diagnosis records in our ED. We anticipate that a future multicenter prospective study will elucidate the prevalence of seizures associated with hypoglycemia in all patients experiencing seizures.

CONCLUSION

Approximately 5% of patients with hypoglycemia in the ED present with seizures. Blood glucose levels in patients with hypoglycemia with and without seizures did not differ significantly.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

Approval of the research protocol: The study protocol was approved by the Institutional Review Board of the Kurashiki Central Hospital.
Informed consent: The participants were free to opt out of the study, as described in the study information on our website. The need for informed consent was waived owing to the retrospective design of the study.
Registry and the registration no. of the study/trial: 4044.
Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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