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Early central diabetes insipidus: An ominous sign in post–cardiac arrest patients

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ABSTRACT

Purpose: Central diabetes insipidus (CDI) after cardiac arrest is not well described. Thus, we aim to study the occurrences, outcomes, and risk factors of CDI of survivors after out-of-hospital cardiac arrest (OHCA).
Materials and methods: We retrospectively analyzed post-OHCA patients treated at a single center. Central diabetes insipidus was retrospectively defined by diagnostic criteria. One-month cerebral performance category (CPC) scores were collected for outcomes.
Results: Of the 169 patients evaluated, 36 patients (21.3%) were diagnosed with CDI. All CDI patients had a poor neurologic outcome of either CPC 4 (13.9%) or CPC 5 (86.1%), and CDI was strongly associated with mortality. Age (odds ratio [OR], 0.96; 95% confidence interval [CI], 0.93-0.99), respiratory arrest (OR, 6.62; 95% CI, 1.23-35.44), asphyxia (OR, 9.26; 95% CI, 2.17-34.61), and gray to white matter ratio on brain computed tomogram (OR, 0.88; 95% CI, 0.81-0.95) were associated with the development of CDI. The onset of CDI was earlier ($P < .001$) and the maximum 24-hour urine output was larger ($P = .03$) in patients with worst outcomes.
Conclusions: All patients diagnosed with CDI had poor neurologic outcomes, and occurrence of CDI was associated with mortality. Central diabetes insipidus patients with death or brain death had earlier occurrence of CDI and more maximum urine output.

1. Introduction

Since the 2010 American Heart Association guidelines, post–cardiac arrest critical care including temperature management has been emphasized as the fifth chain of survival [1]. Despite these efforts in patients with return of spontaneous circulation (ROSC) after out-of-hospital cardiac arrest (OHCA), many patients still show poor neurologic outcomes [2–4]. During multifaceted efforts for better critical care and survival, we came across patients diagnosed with central diabetes insipidus (CDI) and conventionally expected that the neurologic outcome would be poor based on prior experience and studies from other brain injury etiologies because not much evidence exists about the subject.

Central diabetes insipidus due to antidiuretic hormone deficiency is commonly caused by severe trauma or injury in the neurohypophyseal area and is characterized by polyuria, hypernatremia, and hyperosmolar dehydration. Previous studies of traumatic brain injury and other brain injury etiologies show that the incidence of CDI ranges from 3% to 26% [5–8], and diagnosis of CDI is known to be a notorious sign with a high mortality of 69% to 85% [7–9]. Post–cardiac arrest patients may have injury to the hypophyseal pituitary axis, especially as the pituitary is supplied by small branches that may be prone to ischemia during cardiac arrest [10–13]. In addition, cardiac arrest may cause severe brain injury and induce cerebral edema resulting in downward pressure on the hypothalamus and pituitary gland, causing CDI [7].

Some case reports and case series have reported CDI in cardiac arrest [10,14–18]. However, to our knowledge, there were no studies examining CDI in a homogenous group of patients after cardiac arrest. We hypothesize that the contribution of CDI to poor neurologic outcome would be as significant as in other brain injury etiologies. Therefore, we analyzed the occurrences, outcomes, and risk factors of CDI in out-of-hospital post–cardiac arrest patients who were treated with therapeutic hypothermia (TH).

2. Materials and methods

This study was approved by the Samsung Medical Center Institutional Review Board (file number 2015-02-030), and informed consent was waived because the study was based on a retrospective analysis of collected data.

2.1. Study population

This was a single-center, retrospective cohort study of Emergency Medicine–admitted patients for post–cardiac arrest care after OHCA at

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Samsung Medical Center, a tertiary teaching hospital with 70,000 visits annually. All adult OHCA patients (≥18 years) who could not obey after ROSC and admitted to the intensive care unit for post–cardiac arrest care with TH were included. Following admission, we performed protocol-based TH with a target temperature of 33°C, 24-hour maintenance, and a rewarming rate of 0.15°C/h as described previously [19]. The exclusion criteria for TH were severe sepsis, trauma, hemorrhagic shock, and intracranial hemorrhage as the cause of arrest; expected survival less than 3 months before cardiac arrest; more than 12 hours of delay of post–cardiac arrest treatment after ROSC; and old age (>85 years). We also excluded patients who died within 2 days of cardiac arrest because their neurologic outcome could not be fully evaluated, cases in which families refused further treatment, and patients diagnosed with water-sodium balance disorder before cardiac arrest or who had hypertonic saline infusion during treatment.

2.2. Data collection

We collected data from the hypothermia database of out-of-hospital post–cardiac arrest patients treated with TH between January 2010 and March 2015. The hypothermia database is a prospective database of OHCA patients treated with TH and includes Utstein-style data, hypothermia data, and 1-month neurologic outcome. We retrospectively collected other data including demographics from patients' medical records. Diagnosis of CDI was retrospectively defined by objective diagnostic criteria. Laboratory data such as serum sodium and creatinine, spot urine sodium and osmolality, hourly and 24-hour urine output, and treatment of desmopressin were obtained from electronic medical records. Initial brain computed tomograms (CTs) of study patients that were obtained within 6 hours of ROSC were also retrospectively reviewed by 2 emergency physicians blinded to patient outcomes to evaluate the presence of brain edema [20].

2.3. Definition

We defined *CDI* as urine output greater than 300 mL/h for at least 2 hours, hypernatremia (serum Na >145 mmol/L), high serum osmolarity (>300 mOsm/kg), and low urine osmolality (<300 mOsm/kg) [7,8,21,22]. Neurologic outcome was expressed as cerebral performance category (CPC) score. *Poor neurological outcome* was defined as CPC score of 3 (severe neurological disability), 4 (persistent vegetative state), or 5 (death); and *good neurological outcome*, CPC 1 or 2 (absent, mild, or moderate neurological disability) [4]. Glasgow Coma Scale was excluded from the Sequential Organ Failure Assessment score (SOFA) score as the neurologic function does not imply organ failure because of deep sedation of patients after cardiac arrest. *Initial body temperature* was defined as the tympanic body temperature at the time of the decision to perform TH, *time to initiation* was defined as ROSC to cold saline infusion, and *time to target temperature* was defined as ROSC to the time that the esophageal temperature was less than 33.5°C.

The average gray to white matter ratio (GWR) was assessed as documented in previous studies [20]. The obliteration of gray matter and white matter results in lower GWR and indicates presumed brain edema. Hounsfield unit (HU) values measured at the caudate nucleus, putamen, corpus callosum, and posterior limb of the internal capsule were used to calculate the GWR basal ganglia, and HUs at the gray and white matter in the centrum semiovale level and at the gray and white matter in the high convexity level were used to calculate the GWR cerebrum. Average GWR was the average of GWR basal ganglia and GWR cerebrum.

We defined the clinical data as follows. *Maximum sodium level* was defined as the highest sodium level during the hypernatremia period. Spot urine sodium, spot urine osmolality, and serum creatinine were spot laboratory test results collected when CDI was clinically suspected. The day of diagnosis of CDI from the day of cardiac arrest within 24 hours after ROSC was considered day 1. *Duration of CDI* was defined as the number of days from the day of desmopressin nasal puff use to the day that the sodium level normalized at less than 145 mmol/L. *Maximum 24-hour urine output* was defined as the maximum urine output over 24 hours during the hypernatremia period.

2.4. Outcome measures and statistical analysis

We examined the baseline characteristics and neurologic outcome of CDI patients and non-CDI patients. We described nominal variables as numbers and percentages. We described continuous variables as means and standard deviations or median and interquartile range depending on whether or not the variable was in accordance with normal distribution. We used the χ^2 test or Fisher exact test for nominal variables and used the *t* test or Mann-Whitney *U* test for continuous variables. Logistic regression model analysis was performed to assess the diagnosis of CDI and its association to mortality (CPC 5; death and brain death). All variables other than age and sex with a significance level less than .2 in univariate analyses were included in the multivariate logistic regression model. Backward selection was used to determine variables for predicting mortality and risk factors of developing CDI. A subgroup analysis of patients that were diagnosed with CDI by neurologic outcome was done. A *P* value less than .05 was considered

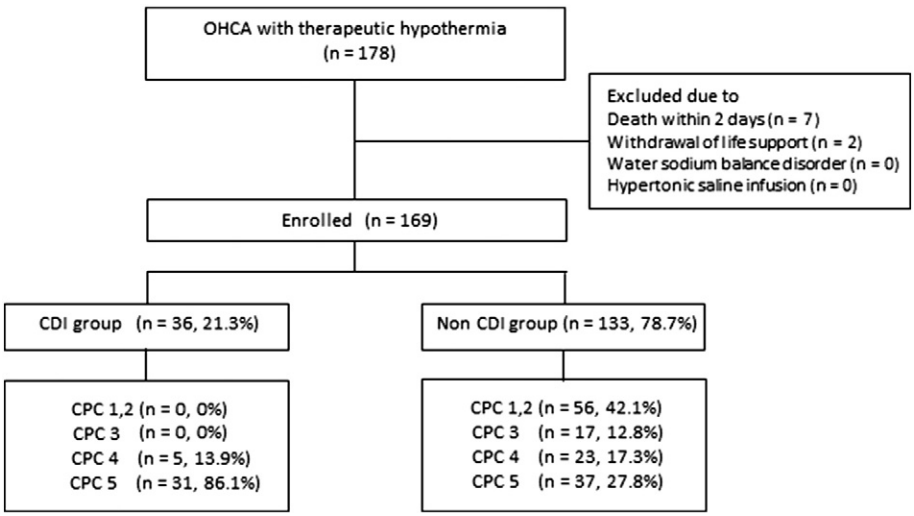

Fig. 1. Study enrollment.