Low Morbidity and Mortality in Children with Diabetic Ketoacidosis Treated with Isotonic Fluids

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Objective To assess current rates of complications of diabetic ketoacidosis (DKA), particularly cerebral edema, in a large tertiary-care pediatric hospital with a consistent management protocol.

Study design We report our single-center retrospective experience with 3712 admissions with DKA in 1999-2011. Our DKA protocol features a "3-bag" system using 2 bags of rehydration fluids, identical except for the presence in 1 bag of 10% dextrose, to allow rapid adjustment of glucose infusion rate. The third bag contains insulin. Fluids are administered at a total rate of 2-2.5 times "maintenance" fluid requirements. Total electrolyte concentration is kept approximately isotonic. Billing and medical records databases at Children's Medical Center Dallas were examined for cases of DKA, cerebral edema, other morbidities, and death.

Results We ascertained 20 cases of cerebral edema (0.5%). Most presented early (median duration of treatment 2 hours). Only 10 of 20 computed tomography scans were graded as moderate edema or worse. Only 10 patients received treatment other than routine DKA management. There was 1 death in a patient with sickle cell trait who developed intravascular sickling. Two patients had neurologic sequelae at hospital discharge but both recovered fully.

Conclusions Compared with data in recent consensus statements, the Dallas protocol is associated with extremely low rates of death and disability (0.08% vs 0.3%) from DKA. *(J Pediatr 2013;163:761-6)*.

Diabetic ketoacidosis (DKA) is the most common reason for hospitalization of children with type 1 diabetes after initial diagnosis, occurring ~1-10 times per 100 patient-years.[1] It is the result of insulin deficiency, as occurs in patients with newly diagnosed diabetes or in situations of poor compliance with the diabetes regimen, often in the context of intercurrent illness. Treatment of DKA requires intravenous administration of insulin and correction of fluid and electrolyte losses with appropriate intravenous fluids. Cerebral edema is one of the most feared complications of DKA. If severe, it can result in brain herniation, with a significant risk of death or permanent neurologic damage. The most recent large clinical series from the US (which includes 1 Australian center)[2] and from the United Kingdom,[3] as well as recent reviews[4] and consensus statements,[1,5,6] all cite a prevalence of 0.5%-0.9% of cases with DKA and state that this complication accounts for 60%-90% of DKA mortality and that the risks of death and permanent disability are 20%-25% and 10%-25% of cerebral edema cases, respectively.

The causes of cerebral edema are incompletely understood. Retrospective studies[7] suggested that rates of fluid administration exceeding 4 L/m^2/24 h were associated with an increased risk of cerebral edema, but more recent studies,[2,3] including a small randomized controlled trial,[8] have failed to show correlations between the development of cerebral edema and fluid administration rates. Current protocols[1,5,6] call for rates of ~3 L/m^2/24 h. In 2000, we described our experience with a DKA protocol we instituted in 1997,[9] distinguished by a "3-bag" system with 2 bags of rehydration fluids—identical except for the presence in 1 bag of 10% dextrose (the third bag contained insulin)—to facilitate rapid and continuous adjustment of net glucose concentration in the administered fluids to control the rate of decrease of blood glucose concentration.

Methods

This study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center. Hospital billing databases were examined as far back as possible (January 1999) for admissions of ≥1 day's duration with *International Classification of Diseases, Ninth Revision* (ICD-9) diagnoses of 250.1x (where x equals an integer).

These admissions were searched for ICD-9 codes of 348.x (cerebral edema, compression of brain) or 96.x (intubation, ventilation). The medical records database was searched for deaths with an ICD-9 code of 250.xx (diabetes of all types). All records on patients with admitting diagnoses of 250.1x were examined individually if the billing database indicated an intensive care unit admission and computed tomography (CT) scanning and/or magnetic

ADA	American Diabetes Association
CT	Computed tomography
DKA	Diabetic ketoacidosis
ICD-9	*International Classification of Diseases, Ninth Revision*
NaCl	Sodium chloride

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resonance imaging. We excluded cerebral edema cases and/or deaths where the patients were not in DKA or had preexisting complicating conditions.

In comparing the Dallas protocol[9] with the 2006 American Diabetes Association (ADA) consensus,[5] we assumed for the former a single intravenous fluid bolus of 20 mL/kg 0.9% NaCl over 1 hour and subsequent fluid replacement with 0.675% NaCl and 49 mEq/L potassium at 3.75 L/m^2/24 h. For the ADA protocol, we assumed a single fluid bolus of 10 mL/kg 0.9% NaCl over 1 hour, then 0.9% NaCl and 49 mEq/L potassium for the next 3 hours at 3 L/m^2/24 h, and then 0.45% saline with 49 mEq/L added potassium at the same rate for the remainder of 24 hours (note that both protocols specify adding 20 mmol/L each of potassium chloride and potassium phosphate; the latter reagent is a mixture of monobasic and dibasic potassium phosphate, and contains 1.47 mEq of potassium per mmol).

Demographics were compared using χ^2 tests, age by t tests, and admission frequencies by Mann-Whitney tests. Outcomes were compared with use of χ^2tests.

Results

There were 3712 admissions to Children's Medical Center Dallas in 1999-2011 with ICD-9 codes of 250.1x, denoting DKA (Table I). These admissions involved 2346 unique patients; 538 patients accounted for 1902 admissions. Of these 2346 patients, 150 (6% of the total) were admitted ≥4 times and accounted for 1014 admissions (27% of all admissions), and 22 patients accounted for 305 admissions. Sex did not represent a risk factor for multiple admissions, but ethnicity did, with African Americans being twice as likely to have >1 episode of DKA than either whites or Hispanics (generally Mexican Americans in our population).

Of 100 random admissions with DKA, 66 were managed on our DKA protocol; the remaining patients had milder acidosis and were managed with intravenous fluids and subcutaneous insulin. In our hospital, patients with a routine case of DKA are admitted to a specialized endocrinology floor, but there were 358 intensive care unit admissions and 229 patients underwent CT scanning.

We considered a patient to have cerebral edema if the patient was in DKA and either cerebral edema was diagnosed on a CT scan or the patient received any treatment for altered mental status other than routine DKA management (Table II). Using these criteria, we ascertained 20 cerebral edema cases in 19 patients among the 3712 admissions (0.5%). Age, race, sex, and newly diagnosed diabetes were not risk factors for cerebral edema (Table I). However, the patients with cerebral edema were admitted more often over the study period, a median (IQR) of 2 (1-4) times, versus all other patients (median and IQR of 1 admission, $P < .0001$).

All 20 patients underwent CT scanning for altered mental status (16 patients) and headache, seizure, suspected cerebral edema, and hyperglycemia (1 patient each). Fourteen CT scans were performed within 3 hours of arrival in the referring hospital or our hospital's emergency department (Figure). Of the 20 scans, 3 were read as normal, 7 as having mild cerebral edema (3 of which were originally read as normal and reclassified after subsequent review by the attending radiologist), and 7 as moderate or ungraded. Three scans had additional findings (herniation, hemorrhage, thrombosis).

Only 10 of the 20 patients received any treatment other than routine DKA management. Seven received such treatment at the referring hospital or in our emergency department. Eight patients were intubated, and 7 patients received intravenous boluses of mannitol. Six patients had both interventions (including the 3 patients who subsequently had normal CT scans). Three patients required placement of ventricular drains.

There was 1 death of a patient with DKA in 13 years (0.03%; 5% of cerebral edema cases): a 13-year-old obese African American girl who presented in a markedly hyperosmolar state with a blood glucose level of 1483 mg/dl and pH 7.16. She had sickle cell trait. Her autopsy showed no cerebral edema, but instead disseminated intravascular sickling that was judged to be the cause of death. Two patients had neurologic sequelae at hospital discharge. One was a 2-year-old patient with cerebral edema and herniation. He made a gradual recovery and is stated as having good school performance in the ninth grade; he has attention-deficit disorder and is treated with atomoxetine. The other patient was an 8-year-old boy who had a posterior cerebral artery infarct. He also recovered gradually, has no apparent permanent sequelae, and is in the 11th grade.

We examined subsequent outpatient records for the remaining patients with cerebral edema to identify possible cognitive sequelae. Comments on school performance were available for 12 of 17 patients; all were reported as having satisfactory school performance, and thus far 5 have graduated from high school.

Table I. Demographic and biochemical characteristics of cases of DKA and cerebral edema

	All DKA cases (N = 3712)	Cerebral edema cases (n = 20)	*P*
Age, mean ± SD, y	11.3 ± 4.2	11.1 ± 4.2	NS
Sex, No. (boys/girls)	1769 (48%)/1923 (52%)	7 (35%)/13 (65%)	NS
Race, % (white/African American/Hispanic/other)	1830 (49%)/1019 (27%)/649 (17%)/194 (5%)	7 (35%)/7 (35%)/4 (20%)/2 (10%)	NS
New diagnoses, No.	1888 (51%)	6 (30%)	NS
Admissions, median No. (IQR)	1 (1-1)	2 (1-4)	<.0001
Initial pH, median (IQR)*	7.25 (7.15-7.33)	7.07 (6.99-7.13)	<.0001
Initial glucose, median (IQR), mg/dl*	389 (313-552)	530 (414-856)	<.0001

NS, Nonsignificant.
*Biochemical statistics determined on a random sample of 100 patients with DKA, and all cerebral edema cases.