Cerebral Edema in Childhood Diabetic Ketoacidosis

Natural history, radiographic findings, and early identification

OBJECTIVE — Children who develop cerebral edema (CE) during diabetic ketoacidosis (DKA) exhibit definable signs and symptoms of neurological collapse early enough to allow intervention to prevent brain damage. Our objective was to develop a model for early detection of CE in children with DKA.

RESEARCH DESIGN AND METHODS — A training sample of 26 occurrences of DKA complicated by severe CE and 69 episodes of uncomplicated DKA was reviewed. Signs of neurological disease were incorporated into a bedside evaluation protocol that was applied to an independent test sample of 17 patients previously reported to have developed symptomatic CE during treatment for DKA. Head computed tomograms and their reports were reviewed.

RESULTS — The protocol allowed 92% sensitivity and 96% specificity for the recognition of CE sufficiently early for intervention. The diagnostic criteria were fulfilled in two temporal patterns, defining early- and late-onset CE. Although initial computed tomograms were often normal, the findings also included diffuse CE and focal brain injury, the latter only in patients with an early onset of abnormal neurological signs.

CONCLUSIONS — CE may occur in the absence of acute changes on head computed tomograms. Early detection of CE at the bedside using an evidence-based protocol permits intervention in time to prevent permanent brain damage.

Diabetes Care 27:1541–1546, 2004

Most children with diabetic ketoacidosis (DKA) exhibit abnormal neurological function. Therefore, evidence-based guidance for discerning the patients who require lifesaving intervention is needed. Cerebral dysfunction in DKA is usually a manifestation of metabolic derangement, but cerebral edema (CE) arises in ~1% of episodes and is a complication that frequently causes irreversible brain damage and death (1–7). Neurological collapse from CE is typically described as having sudden onset and progressing rapidly, with recovery depending on prompt reduction of intracranial pressure (4.8–10). The object of this study was to delineate the signs and symptoms of neurological compromise that predict progression to severe CE in children with DKA.

CE occurs rarely in patients older than age 20 years (8,11,12), despite the presence of asymptomatic CE in most adults and children with DKA (13–16). This age dependence may point to developmental changes in cerebral metabolism as critical elements in the pathogenesis of CE. For example, children’s brains are reported to have higher fuel and oxygen requirements than those of adults (17,18). Hypoxia is further implicated because the brains of patients with DKA may extract blood oxygen less efficiently than healthy individuals (16) and the reported association of symptomatic CE with low partial pressures of carbon dioxide in arterial blood may reflect harmful cerebral vasoconstriction (5,6). Exuberant rehydration with hypotonic fluid and bicarbonate administration may aggravate the CE (5,6,9,11,12,19–22); however, the evidence that CE is primarily iatrogenic is not compelling (6,8,23–29). In the absence of an understanding of the pathogenesis of CE and its prevention, emphasis must be on early recognition of the disease to permit quick intervention, with the hope of reducing morbidity and mortality (4.8–10).

RESEARCH DESIGN AND METHODS — The College of Medicine Institutional Review Board granted an exemption for written consent. Medical records of 24 previously unreported patients (ages 1–15 years) who had CE during treatment of DKA at various hospitals in the U.S. were reviewed. All patients had poor outcomes, and the records were originally acquired between 1990 and 1999 for analysis during litigation. Two patients who were seen for CE during treatment of DKA at our institution, Shands Hospital, were also included. The Shands Hospital database for 1990–1999 identified 69 consecutive episodes of uncomplicated DKA in 58 children who had an episode before age 13 years. Recurrent episodes (n = 11) provided comparative data for CE case subjects up to age 15 years.

The diagnosis of DKA required a clinical history consistent with diabetes, a venous or arterial pH < 7.30 or a serum total CO₂ < 15 mmol/l, and an elevated serum concentration of β-hydroxybutyrate or ketonuria > 80 mg/dl on a urine test strip. CE was diagnosed when a patient being

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Received for publication 12 December 2003 and accepted in revised form 1 April 2004.

Abbreviations: CE, cerebral edema; CT, computed tomography; DKA, diabetic ketoacidosis; ROC, receiver-operating characteristic.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances. © 2004 by the American Diabetes Association.
Cerebral edema in DKA

Table 1—Bedside evaluation of neurological state of children with DKA

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>Major criteria</th>
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<tbody>
<tr>
<td>Abnormal motor or verbal response to pain</td>
<td>Altered mentation/fluctuating level of consciousness</td>
</tr>
<tr>
<td>Decorticate or decerebrate posture</td>
<td>Sustained heart rate deceleration (decline more than 20 bpm) not attributable to improved intravascular volume or sleep state</td>
</tr>
<tr>
<td>Cranial nerve palsy (especially III, IV, and VI)</td>
<td>Age-inappropriate incontinence</td>
</tr>
<tr>
<td>Abnormal neurogenic respiratory pattern (e.g., grunting, tachypnea, Cheyne-Stokes respiration, apneusis)</td>
<td>Minor criteria</td>
</tr>
<tr>
<td>Pertonic mannitol infusion, was associ-</td>
<td>Vomiting</td>
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<tr>
<td>tion for neurological symptoms began for</td>
<td>Headache</td>
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<tr>
<td>cerebral edema in a head computed tomography (CT) scan, or resulted in death or permanent neurological damage from no other definable cause.</td>
<td>Lethargy or being not easily aroused from sleep</td>
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<tr>
<td></td>
<td>Diastolic blood pressure &gt; 90 mmHg</td>
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<td></td>
<td>Age &lt; 5 years</td>
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Signs that occur before treatment should not be considered in the diagnosis of cerebral edema.

treated for DKA and who had no history of neurological disease had severe neurological findings (e.g., coma, posturing, seizures, cranial nerve palsies, respiratory failure) that responded promptly to hypertonic mannitol infusion, was associated with edema on a head computed tomography (CT) scan, or resulted in death or permanent neurological damage from no other definable cause.

In this study, t = 0 was the start of intravenous fluid administration. Heart rate, blood pressure, respiratory rate, neurological status, and all notes reporting abnormal progress were documented. Reports of radiographic studies of the head (n = 23) were reviewed by a neuroradiologist, as were all available films (n = 11).

Outcome at the time of discharge was recorded as no permanent morbidity (n = 1), mild permanent morbidity (n = 0), severe permanent morbidity (n = 9), or mortality (n = 16) (8).

Cases and control subjects were matched for age (within 3 years), initial serum osmolality (within 15 mOsm/kg), and total CO₂ concentration (0–5, 6–10, or 11–15 mmol/l). The time the intervention for neurological symptoms began for the case subject was the time used for analysis of data from matched control subjects.

The signs of distress given in Table 1 were weighted as having diagnostic, major, or minor significance based on an estimate of the positive predictive value for serious neurological disease. Thus, signs of neurological collapse (e.g., pupil changes) that needed no further evidence to prompt consideration of specific therapy for raised intracranial pressure were considered diagnostic. Signs that occurred frequently in the complicated case subjects, but rarely in control subjects, and that were considered reliable clinical signs of neurological dysfunction were designated as major criteria. Signs that occurred more frequently in case than in control subjects, but were present in both populations or were considered less specific indicators of neurological disease were rated as minor criteria. A more objective method for risk assignment would require a larger sample.

To be applied toward the diagnosis of CE, each criterion had to be observed after the rapid infusion of fluid was changed to a slower rate and before the need for resuscitation was recognized. For example, vomiting before and during the initial treatment of DKA was discounted. If emesis began after the patient had received a fluid bolus and had taken nothing by mouth since starting treatment, it was counted as a minor criterion for diagnosis. Heart rate decelerations (decline of > 20 bpm) had to be of sudden onset, persistent (recorded in the nursing record on at least two successive entries that were separated by at least 15 min), and unrelated to sleep or rapid fluid replacement. Heart rate did not have to be truly bradycardic (i.e., < 60 bpm). Incontinence was not diagnosed if the patient had primary enuresis or another cause of chronic incontinence, and lethargy was not considered present if the patient could be easily aroused from sleep.

The criteria derived from the training dataset were prospectively applied to an independent set of children whose course of complicated DKA has been published elsewhere (8). Complete records were still available for re-review of 17 case subjects.

Results from the study are given as means ± SD.

RESULTS—The matched analysis included 62 control subjects (1–4 control subjects per case). Information from seven episodes involving seven female patients could not be matched to that of a case subject. Of the 26 case subjects with CE, 4 (15%) began their treatment at a tertiary care facility and 3 (12%) were transferred to centers offering higher levels of care before neurological symptoms developed. Of the 62 control cases, 36 (58%) were treated in another hospital before being transferred. The age, sex, duration of diabetes, and initial serum concentrations of glucose, sodium, osmolality, total carbon dioxide, and blood pH of the case and control patients at the time of admission were not significantly different. Sample bias prevented a systematic comparison between complicated and uncomplicated cases of DKA. Nonetheless, there were no differences in the fluid volumes provided to the two matched groups. The fluid volume during the resuscitation phase in case subjects was 15 ± 6 vs. 20 ± 12 ml·kg⁻¹·h⁻¹ for control subjects. The total fluid volume from t = 0 until the CE could be diagnosed (using criteria in Table 1) was 11 ± 4 ml·kg⁻¹·h⁻¹ in the children with CE and 10 ± 5 ml·kg⁻¹·h⁻¹ in matched control subjects.

Bedside evaluation of neurological state

The average time from the start of treatment to recognition of neurological collapse in the patients with CE was 9.6 ± 6.7 h (range 2.5–30 h). Classic signs of neurological distress were usually apparent, however, before collapse occurred. The mean interval from the time patients met diagnostic criteria until the time they experienced a neurological collapse was 3.1 ± 2.6 h (range 0–11 h).

The receiver-operating characteristic (ROC) curve (Fig. 1) demonstrated optimal estimates of sensitivity (92%) and specificity (96%) for the early diagnosis of CE in the presence of one diagnostic criterion (n = 7 CE case subjects), two major
**Figure 1—** ROC curve of diagnostic criteria for cerebral edema. The ROC curve plots sensitivity against the false-positive rate. The ideal discriminator would plot at 1.0 on the ordinate and 0 on the abscissa. The plot shows how increasing the stringency of the threshold for diagnosis of CE decreases both the sensitivity and the false-positive rate (i.e., increases the specificity). As the criteria for the diagnosis become progressively more stringent (e.g., one major to one major + one minor to one major + two minor to one major + three minor; one major to two major to three major), the specificity is increased and the sensitivity is decreased. For this analysis, only those clinical criteria that were charted before the need for resuscitation was recognized were included as early identifiers of CE. All patients with poor outcomes eventually displayed signs classified in the diagnostic category, but not necessarily before the need for resuscitation was recognized. When applied to the 26 case subjects and 69 control subjects, the appearance of one diagnostic criterion (n = 7), two major criteria (n = 11), or one major + two minor criteria (n = 6) yielded a sensitivity of 92% and a false-positive rate of 4%.

**Figure 2—** Onset of neurological signs of CE has a bimodal distribution in time. Despite the large fluid volumes that were routinely provided to children treated during the 1970s and 1980s, the CE patients reviewed here and those cases previously published by Rosenbloom both demonstrated distinct early and late times of onset of neurological impairment.

**Clues to the pathogenesis of CE**

The time from treatment onset to when the criteria for neurological compromise were met fell into a bimodal distribution (Fig. 2). Of the training sample, 17 patients (65%) met the diagnostic criteria 3.2 ± 1.5 h (range 0–6) after starting treatment; the remaining patients met the diagnostic criteria 14.3 ± 4.5 h (range 10–24) after starting treatment. A bimodal distribution of time to CE diagnosis was also present in the test sample of 17 case subjects (8). Children in the early-onset group tended to be older (r = -0.28) than those with a later onset of neurological collapse (P = 0.09, Spearman rank correlation).

Of the 26 case subjects with CE, radiographic studies were done in 23 (16 early onset, 7 late onset). The initial head CT scans were performed 8.6 ± 8.5 h (range 2–44) after the diagnostic criteria for CE were met; all the patients were profoundly symptomatic while being studied. Of the 23 patients, 2 (39%) had no acute brain abnormalities visible, 6 (26%) showed diffuse CE, 4 (17%) demonstrated subarachnoid or intraventricular hemorrhages, and 3 (13%) had both edema and hemorrhages. Focal brain injury in the mesial basal ganglia and thalamus, the periaqueductal gray matter, and the dorsal pontine nuclei were observed in five subjects (22%). These localized injuries were found only in the early-onset patients. This selectivity was not an artifact of the time that the studies were performed, because images of the brains of patients with early- and late-onset CE were obtained at 9.9 ± 5.9 and 6.4 ± 2.5 h, respectively, after the diagnostic criteria were fulfilled.

**CONCLUSIONS**— Abnormal neurological signs and symptoms are common in children with DKA and do not always demand specific treatment. The clinician’s decision to intervene is a par-
ticularly difficult one because early treatment may be critical in preventing neurological demise (4, 8–10). Therefore, the application of validated clinical criteria for the early diagnosis of CE may reduce the mortality and severe morbidity caused by this complication. New medical practices are more likely to be implemented when they simplify the process of providing care to patients (30). The bedside evaluation proposed here meets this standard and was validated with an independent test sample of CE patients.

Because the bedside evaluation emphasizes early recognition of CE, frequent and skilled nursing assessments are absolutely necessary. A tertiary or special care setting is usually required to ensure the immediate availability of pediatric specialists. The physician must specifically ensure that nurses are aware of the importance of neurological monitoring of children with DKA, especially if the nurses are accustomed to treating ketoacidotic adults who are not prone to CE. Reliance solely on the Glasgow coma scale is inappropriate. The children’s cases reviewed in this study often showed clinically relevant signs of neurological compromise (e.g., incontinence, vomiting, headache, heart rate deceleration), despite minimal or no changes in their Glasgow coma scale rating.

The current treatment for suspected CE is immediate infusion of hypertonic mannitol at dosages as high as 1 g/kg body wt and to restrict fluids (31). Endotracheal intubation may be needed to protect the airway of the comatose patient, but the value of hyperventilation is questionable. Other pharmacological and surgical measures for intracranial hypertension have no proven benefit in treating CE complications of DKA, although improvement after hypertonic saline infusion has been reported (32).

Application of the suggested clinical criteria, which had an estimated specificity of 96%, will result in unnecessary treatment of some children. The most frequently cited incidence of CE is 1% of DKA episodes, an observation recently confirmed in a study (6). Thus, the protocol’s positive predictive value reveals that five children will be treated for every one who is likely to progress to a poor outcome if left untreated. The extent of morbidity that might result from the administration of hypertonic mannitol is unknown, but we found no published reports of adverse effects in children with DKA who survived an episode of CE. In particular, the risk for acute renal failure, rebound CE, pulmonary edema, hyperkalemia, transient hypotension, and anaphylaxis must be considered, but kept in perspective. Untreated CE can progress rapidly to an irreversible situation.

This study included examination of predominantly litigated case subjects with CE. Similar outcomes to ours were reported in studies where selection bias for the worst outcomes was not present (1, 33). Even in the largest, most modern series from 10 pediatric centers, 21% of patients with CE had permanent neurological dysfunction and 21% died (6). The lower morbidity and mortality in more recent studies may represent less stringent definitions of clinically important CE. Thus, many patients with spontaneously reversible disease may have been included.

The application of this assessment to clinical practice should be uncomplicated. The format is familiar, reminiscent of the Jones criteria for diagnosing rheumatic fever (34). The assessment requires no laboratory studies. Physicians and nurses can perform the assessments reliably, safely, rapidly, and frequently, and the results of the assessments can be easily and unambiguously documented.

The minimum duration that a sign or symptom must be present to make the diagnosis of CE could not be strictly defined in this study. In addition, a more rigorous method for designating the risk of the various signs is desirable. These will be best determined with the accumulation of more experience in the prospective trial required to validate the criteria.

The data from this study allow some comment on the pathogenesis of CE. Correlates of CE have been reported to include the changes in serum osmolality, pH, glucose, and sodium concentrations induced by DKA treatment (4–6, 9, 15). Consequently, CE has been attributed to the retention of intracellular osmolytes in the brain during rehydration, causing a shift of water into the intracellular space. This hypothesis is the basis for current fluid-management standards in children with DKA that suggest rehydration be accomplished gradually over 48 h (31). Nonetheless, fluid replacement with hypotonic solutions at rates and in volumes that exceed the recommendations still frequently occurs (35). Most of the children who receive such treatment do not develop CE. Conversely, CE occurs in children whose care meets contemporary standards.

This study substantiates the hypothesis that CE has a multifactorial etiology. The bimodal distribution of the time of onset of clinically significant neurological dysfunction may reflect different pathological processes. The discordance in some patients between their radiographic abnormalities and their severe neurological impairment is important. Of the patients in coma, ~40% showed no acute abnormalities on their initial CT exams, emphasizing that CE in the context of DKA is a clinical, not a radiological, diagnosis. Subsequent studies of these same patients often showed diffuse edema, hemorrhage, and infarction. These results are similar to those previously reported (6, 8). The dissonance between the radiographic and clinical signs suggests that CE may arise as a consequence of another, as yet unrecognized, neurological insult. Indeed, the pattern of focal injury in the mesial basal ganglia and thalamus, the periaqueductual gray matter, and the doral pontine nuclei suggests a primary metabolic insult in at least some patients, because these are areas of high ATP demand. The distribution of the lesions is inconsistent with either diffuse transcompartamental water flux or vaso-occlusion as primary etiologic factors. The exclusive appearance of this focal injury in patients with early-onset CE further suggests a distinction in the causes of CE between those with early and those with late onset of symptoms.

The incidence of CE in children with DKA has not changed over the past 15–20 years (1–3, 6, 7), despite the widespread introduction of gradual rehydration protocols during this interval. This study confirmed the previously published observation that radiographic imaging is frequently unhelpful in making the diagnosis of CE immediately after presentation of symptoms (8). An evidence-based protocol for bedside neurological evaluation of all pediatric patients with DKA has therefore been proposed. The value of this clinical assessment is predicated on the hypothesis that early treatment of CE is potentially lifesaving. Nonetheless, the diagnostic criteria for CE proposed in this study require prospective validation before they can be considered the standard of care. For now, they provide the first
practical, evidence-based approach to the bedside diagnosis of CE in children with DKA.

APPENDIX

The following case reports describe the two episodes of CE that were not diagnosed by the proposed protocol and the three episodes that met protocol criteria for CE, but resolved without specific intervention.

Patient 1. After ~4.5 h of treatment for DKA, a 10-year-old boy became lethargic (one minor) and answered questions inappropriately (one major). His mental state improved quickly after a 1.5-h hypertonic mannitol infusion was started. Then 3 h later, his Glasgow coma scale score fell from 15 to 8. He was re-treated with mannitol and responded, but more slowly this time. Studies of the serum and cerebrospinal fluid revealed no toxic, infectious, or inflammatory cause of his coma. His head CT and magnetic resonance imaging studies were normal. He recovered over 3 days without permanent sequelae.

Patient 2. After ~4 h of treatment for DKA, an 8-year-old boy became incontinent (one major) and complained of a headache (one minor). He felt better within 30 min, but 5 h later, he was found to be unresponsive, with fixed pupils, bradycardia, and hypertension. He was intubated and given hypertonic mannitol immediately after his collapse. A head CT scan showed diffuse CE. He did not survive.

Patient 3. After 8 h of treatment for DKA, an 8-year-old girl had a diastolic pressure of 92 mmHg (one minor). Her heart rate fell from 120–130 to 98 bpm (one major). Over the next 2 h, her blood pressure remained elevated and she became combative, began making incomprehensible sounds, and would not answer questions (one major). She was incontinent of urine (one major). Her neurological status gradually improved until she was normal 15 h after treatment was begun.

Patient 4. After 8 h of treatment for DKA, a 7-year-old boy’s heart rate fell from 100–114 to 88 bpm and then to 78 bpm (one major). He had one episode of emesis (one minor) and complained of a headache (one minor). He became hard to arouse and had a “glassy stare” (one minor) 1 h later. He was not oriented to place and was described by his nurse as having an “altered level of consciousness” (one major). By this time his heart rate had returned to its previous baseline. Then 3 h later, he was incontinent of urine (one major) and remained weak and lethargic. By 15 h after starting treatment, his mental state was normal.

Patient 5. After 3 h of treatment for DKA, an 11-year-old girl rapidly became disoriented and had confused verbal responses to painful stimulation (one major). At the same time, her heart rate fell from 106–114 to 80 bpm (one major). Her blood pressure remained unchanged. Her level of consciousness improved over the next 4 h. She ultimately recovered completely.

References

Cerebral edema in DKA