

Cerebral edema in diabetic ketoacidosis

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Objective: To review the causes of cerebral edema in diabetic ketoacidosis (CEDKA), including pathophysiology, risk factors, and proposed mechanisms, to review the diagnosis, treatment, and prognosis of CEDKA and the treatment of diabetic ketoacidosis as it pertains to prevention of cerebral edema.

Data Source: A MEDLINE search using OVID was done through 2006 using the search terms *cerebral edema* and *diabetic ketoacidosis*.

Results of Search: There were 191 citations identified, of which 150 were used. An additional 42 references listed in publications thus identified were also reviewed, and two book chapters were used.

Study Selection: The citations were reviewed by the author. All citations identified were used except 25 in foreign languages and 16 that were duplicates or had inappropriate titles and/or subject

matter. Of the 194 references, there were 21 preclinical and 40 clinical studies, 35 reviews, 15 editorials, 43 case reports, 29 letters, three abstracts, six commentaries, and two book chapters.

Data Synthesis: The data are summarized in discussion.

Conclusions: The causes and mechanisms of CEDKA are unknown. CEDKA may be due as much to individual biological variance as to severity of underlying metabolic derangement of the child's state and/or treatment risk factors. Treatment recommendations for CEDKA and diabetic ketoacidosis are made taking into consideration possible mechanisms and risk factors but are intended as general guidelines only in view of the absence of conclusive evidence. (*Pediatr Crit Care Med* 2008; 9:320–329)

KEY WORDS: diabetic ketoacidosis; brain edema; fluid therapy; insulin; child; risk factors

Cerebral edema in diabetic ketoacidosis (CEDKA) has been identified for 70 yrs and has been a subject of much investigation and debate during the 40 yrs since the inception of pediatric critical care medicine. Although many risk factors of both diabetic ketoacidosis (DKA) and its treatment have been identified and have led to many proposed pathophysiologic mechanisms, there is no general agreement concerning the risk factors, pathophysiology, and mechanisms underlying CEDKA, for several reasons. First, variable definitions of symptomatic cerebral edema have been used. Second, there is an absence of adequately powered, prospective, controlled, randomized clinical trials. Most reports are either small, retrospective, uncontrolled, and/or nonrandomized and have resulted in

many interesting but unsubstantiated and conflicting theories. Third, it is inherently difficult to study *in vivo* metabolism and cellular integrity in the human brain. Recently, several technical developments, especially magnetic resonance imaging (MRI) technology, have improved knowledge in this area. Fourth, the pathogenesis may be complex and multifactorial and may proceed in stages, making it impossible to understand by unifocal analysis.

Symptomatic cerebral edema (CE) in pediatric patients with DKA is uncommon and is defined by diagnostic criteria, including abnormal motor or verbal responses to pain, decorticate posture, and abnormal neurogenic respiratory patterns. Major, but not diagnostic criteria include altered mentation, sustained heart rate decelerations, and age-inappropriate incontinence. Minor criteria include vomiting, headache, lethargy, diastolic blood pressure >90 mm Hg, and age <5 yrs (1). Subclinical CEDKA is usually defined by imaging studies and is probably common. Most of the deaths in pediatric patients with type 1 diabetes mellitus (DM) are due to symptomatic CE.

Here I review the risk factors for the disease state and its treatment as well as the proposed pathophysiologic mechanisms, using a combination of a review of

the literature and almost 40 yrs of clinical experience to discuss recommendations for treatment of DKA to prevent symptomatic CE and for treatment of symptomatic CEDKA once it occurs.

Pathophysiology and Risk Factors

Most evidence supporting different risk factors is based on underpowered, retrospective, noncontrolled, and/or nonrandomized clinical studies. Several interesting animal studies are also reviewed, and I will specify risk factors of the disease state itself vs. risk factors associated with treatment.

Hypoxia and Ischemia. Dillon et al. (2) proposed a mechanism based on risk factors having to do with the disease state: a reduced blood volume due to dehydration aggravated by a low P_{aCO_2} , attributable to acidosis and hyperventilation, all leading to vasoconstriction and resulting in cerebral ischemia, hypoxia, and increased capillary permeability as the cause of CEDKA. Increased whole blood viscosity (3) and arrest secondary to electrolyte abnormalities (4) have also been proposed as causes of ischemia. Cerebral hypoxia and ischemia are supported by the work of Glaser and colleagues (5–7), who found significantly higher serum urea nitrogen and lower

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Paco₂ levels in CEDKA patients compared with matched controls. Using the same database, Marcin et al. (8) found a poorer outcome due to disease state risk factors in patients with greater neurologic depression at the time of diagnosis of CE and high initial serum urea nitrogen. Lawrence et al. (9) found some support for this theory with lower initial bicarbonate and higher initial blood urea nitrogen levels in patients with CE. Dunger and Edge (10) and Edge (11) emphasized that evidence supporting this theory is not completely convincing and there are contradictory pieces of evidence as well.

Hyperosmolar State and Fluid Administration. Several authors emphasize the importance of the risk of disease state due to the hyperosmolar state in long-standing hyperglycemia in these patients (10–22) as well as in experimental models in rats (23–25), dogs (26–28), and rabbits (29). The theory is due to the disease state; there is prolonged hyperosmolarity in the serum, and brain cells protect their volume status by producing intracellular osmoles via production of metabolic products thought to be primarily taurine (23, 24, 30) and myoinositol (14, 30, 31). These osmoles dissipate from the intracellular space slowly after serum osmolality begins to decrease, taking hours to days to return to normal due to the characteristics of the organic osmolyte efflux channels and the downregulation of cotransporters, which can take 16 hrs to begin to act after abrupt reduction of extracellular osmolality in rat cortical astrocytes (30). These conditions favor movement of water from the serum into brain cells. Therefore, risks are also associated with therapy with insulin, which lowers blood glucose (18, 32–34) and stimulates the sodium-hydrogen exchange mechanism, increasing intracellular sodium concentration (35, 36) and fluid (especially hypotonic fluid) (12, 37–46) given to repair dehydration. Both of these interventions can cause a rapid decrease in serum osmolality and favor movement of water into brain cells, although the causal relation of fluid administration to CEDKA is debated (5, 47, 48).

Several authors doubt the hyperosmolarity and treatment explanation, pointing to the presence of CE before therapy in some patients as a major contradiction (5, 9, 49–55). Levitsky (44) reminded us that head ultrasonography and computed tomography (CT) scans cannot distinguish between an increase in brain blood

volume due to vasodilation and an increase in brain tissue volume due to CE. Glaser et al. (56) also pointed out that CT scans cannot distinguish between vasogenic edema due to blood-brain barrier endothelial cell injury secondary to ischemia and/or hypoxia and cytotoxic edema due to brain cell swelling secondary to hyperosmolality.

Recent MRI studies have more effectively distinguished these different sites of injury and therefore mechanisms of edema and have indicated that edema may be more vasogenic (blood-brain barrier) than cytotoxic (cellular) in origin. Figueroa et al. (50) performed MRI studies on four patients on admission, at 6–8 hrs, and 120 hrs after therapy began. These studies indicated that CE was present in asymptomatic patients and before therapy was started. Edema was vasogenic in nature, indicating a perturbation of the endothelial cells of the blood-brain barrier, which is a microcapillary abnormality. Injury may be mediated by an inflammatory process as well as metabolic abnormalities and oxidative stress. Glaser et al. (56), also using MRI technology, found vasogenic edema rather than osmotic swelling, and Glaser (57) indicated that this may be due to hypoperfusion and ketone bodies affecting the blood-brain barrier. Those authors also suggested that increases in metabolites, such as taurine and myoinositol, found in some studies may be subsequent to central nervous system cellular injury rather than the original cause of osmotically induced CE.

When we debate 1) whether CE is present in all patients with DKA; 2) whether CE (when present) is vasogenic in nature, indicating blood-brain barrier endothelial cell injury due to ischemia, hypoxia, inflammation, metabolic derangement, or oxidative stress; or 3) whether CE is cytotoxic in nature, indicating the importance of the hyperosmolar state and subsequent therapy with insulin and fluids, it is important to realize no one factor may be solely responsible for the phenomenon and that several factors may be important in a progressive sequence. Levitsky (44) pointed out that the initial response of the central nervous system to the metabolic derangements of the disease state may be vasogenic in nature, with blood-brain barrier perturbation occurring along with later development of symptomatic CE with cytotoxic edema due to other secondary insults, such as fluid administration, dys-

regulation of vasopressin release, sodium bicarbonate administration, and intracellular as well as extracellular fluid accumulation.

The observation has been made (11) that the role of fluid in causing symptomatic CEDKA is puzzling in that the incidence has stayed the same even though much more conservative fluid management is now practiced to prevent excessive free water administration and lack of serum sodium increase during therapy (58, 59). Although that may be true, I find that many patients referred to our unit are initially managed in small local clinics and emergency rooms frequently by physicians trained in adult emergency medicine, and these patients still receive generous amounts of fluid, hypotonic fluids, or both.

Insulin Dosage. In addition to initiating fluid shifts due to relatively increased intracellular central nervous system osmolality after the administration of insulin and a subsequent decrease in serum osmolality (29, 60), insulin may have other effects that cause CE. Using a rat model, Johanson and Murphy (61) stimulated increased choroid cell concentration of sodium with insulin, and this was blocked by acetazolamide, a standard inhibitor of cerebral spinal fluid production. In a rat model in which DKA was induced by streptozotocin, Tornheim (62) found an increase in brain edema with aggressive treatment with fluid and insulin but not with fluid alone. This supported Arieff and Kleeman's (29) findings in a hyperglycemic rabbit model, in which edema did not occur with reduction of serum glucose by peritoneal dialysis but edema did form when hyperglycemia was reduced by insulin.

Blood Glucose Concentration. Investigators have tried to correlate the presence of CE with the rate of decrease in blood glucose (12, 63). As indicated in the hyperosmolar theory, a decrease in glucose could be related to a decrease in serum osmolality, causing fluid shifts into brain cells, and then insulin administration would be a treatment risk factor. Not all studies have found a tight correlation for this factor.

Sodium Bicarbonate Administration. Several authors have implicated the administration of sodium bicarbonate to patients as a treatment risk factor in the development of CE (5, 64, 65). The risk is presumably due to either decreased oxygen delivery to the brain secondary to a shift in the oxygen dissociation curve (43)

resulting in hypoxia, paradoxical cerebral spinal fluid acidosis (66–70), or both. Several authors have stated that sodium bicarbonate is dangerous and should not be used (5, 71, 72) with the possible exception of severe myocardial depression (64) due to acidosis. It is controversial, however, whether severe acidosis causes myocardial depression (64, 73) in DKA patients. Others dispute this prohibition (11, 74) and do not find convincing evidence of sodium bicarbonate as a treatment risk factor for CE.

Intubation and Hyperventilation.

Marcin et al. (8) reported that intubation and hyperventilation as treatment for symptomatic CE were an independent risk factor for a worse outcome. This is consistent with the theory that low Paco_2 levels cause vasoconstriction and ischemic injury to the blood-brain barrier, resulting in vasogenic edema. Tasker et al. (75) argued that patients who are intubated and ventilated for symptomatic CE need to be ventilated at Paco_2 levels lower than the normal range, because ventilation at normal Paco_2 levels represents a sudden increase in patients' Paco_2 from their spontaneous hyperventilation state during DKA and has detrimental effects. Fortune (76), Marcin et al. (77), and Ackerman (78) seem to agree with this, suggesting that patients intubated and ventilated for CE should be ventilated to Paco_2 levels representing their baseline state at the onset of symptoms to avoid either too high or too low Paco_2 levels. Ventilation at Paco_2 levels that may either cause further cerebral vasoconstriction and aggravate ischemia or cause cerebral vasodilation and aggravate increased intracranial pressure (ICP) may be complicated by altered cerebral autoregulation in DKA patients. Hoffman (79), using transcranial Doppler ultrasound in five patients, found an increased pulsatility index, suggesting an increased ICP due to the existence of cerebral vasoparalysis based on low values of cerebral vascular reactivity before treatment and 6 hrs after initiation of treatment. There was a return of vascular tone at 24 hrs with a complete reversal by 48 hrs. Roberts et al. (80), also using a transcranial Doppler, determined that cerebral autoregulation was impaired in five of six patients at 6 hrs and normalized by 36 hrs. There was no ischemia, with all patients having normal to increased cerebral blood flow and increased cerebral oxygenation. Their findings favor a vasogenic mechanism for the formation of

CEDKA. Cerebral vascular dysregulation may be mediated by an increase in prostaglandin I_2 produced from adipose tissue, as found in a DKA rat model (81).

Several authors (82–85) indicate that the risk of CE seems to be related to severity of acidosis and that this is related to 1) the severity of metabolic derangement causing CE; 2) treatment of DKA risk factors, such as receiving sodium bicarbonate; or 3) another risk factor of treatment of CE, such as acute alteration of pH and Paco_2 with intubation and ventilation.

Although many disease state risk factors, as well as treatment risk factors, have been postulated to be associated with or causative in the development of CEDKA, it is not known whether any of them are responsible. Several authors indicate that the risk of developing CEDKA may be due not to treatment factors at all but rather to the severity of metabolic derangement of the disease state (9–11, 40, 74, 86–89) and that development of CE is unpredictable (90–92). In that respect, earlier recognition and treatment of new-onset disease and better management and compliance in known DM patients are probably the best ways to prevent CE (21, 93–95).

Proposed Mechanisms of CEDKA

Accumulation of Intracellular Osmoles. As indicated previously, several lines of evidence in humans (10, 12–22, 58, 59), as well as models of hyperglycemia or DKA in rat (23–25), dog (27, 28), and rabbit (29), implicate generation of intracellular osmoles (“idiogenic”) to protect brain cell volume when serum is hyperosmolar, as in hyperglycemia, as the cause of CEDKA. These intracellular osmoles are now thought to be taurine (23, 24, 30) and myoinositol (14, 30, 31). Acetoacetate (96) and ketones (97) may be implicated in the intracellular hypertonicity in these patients as well. These osmoles dissipate over 12 to 24 hrs after initiation of fluid and insulin therapy to correct dehydration and hyperglycemia (30). Due to the slow dissipation of these intracellular osmolytes, when serum osmolarity decreases rapidly, there is a relative hyperosmolarity in brain cells, favoring a shift of fluid into brain cells. This seems to require the presence of insulin (29, 33, 62).

Role of Vasopressin and Atrial Natriuretic Factor. Vasopressin is elevated in

uncontrolled DM in adults (98) and has been postulated as causative in pediatric patients as well (99). This promotes fluid retention, but the osmotic diuresis in DKA results in a balanced net effect. Once therapy with insulin is begun and the glycosuria is stopped, vasopressin level is still elevated and could cause water intoxication. Vasopressin is required for optimal cell size in the kidney, but it is unknown whether this occurs in the brain. There is no known correlation between vasopressin levels and the degree of brain edema.

Atrial natriuretic factor, which produces natriuresis and excretion of volume via the kidney, is reported to be suppressed in the volume-depleted state in adults with uncontrolled DM (11). The initial low level in children is reported to increase during 24 hrs with therapy. It is possible that this results in elevated atrial natriuretic factor levels, causing natriuresis and hyponatremia and favoring water movement into brain cells after initiation of therapy for DKA.

Sodium/Proton Antiporter and Other Membrane Cotransporters. Sodium-hydrogen exchange mechanisms at the cell membrane are important in regulating intracellular ion concentration and therefore cell volume in many cells, including the brain (30, 100). Sodium-bicarbonate cotransporters (101, 102) and sodium-potassium ion exchange channels (103, 104) are important in this role as well. These channels are affected by many perturbations, including acidosis (100, 105), ischemia (105), insulin (35, 76, 103), vasopressin (98), and even glucose (106) and ketosis (97). Incubation of rat vascular smooth muscle cells in a high-glucose medium for 24 hrs increases sodium-hydrogen exchange channel activity, probably via phosphocreatine kinase activation (106). All of these promote an increase in intracellular ionic concentrations in brain cells, resulting in glial swelling as well as alteration in endothelial cells of the blood-brain barrier favoring vasogenic edema. Lam et al. (105) were able to decrease CE formation in a streptozotocin-induced DKA rat model as determined by MRI scan when giving the sodium-potassium-chloride cotransporter inhibitor bumetanide. In addition to the factors listed previously, use of sodium bicarbonate would buffer protons released from cells into the extracellular space, causing further movement of protons out of brain cells and therefore sodium transport into cells,

thus promoting more water movement into cells.

Hypoxia and Ischemia. In addition to the clinical risk factors already cited (2, 5), activation of excitatory amino acid receptors (N-methyl-D-aspartate) during postischemic, peri-infarct depolarizations is implicated in the mechanism of CE by which the ischemic penumbra is recruited into the core of cerebrovascular stroke. Hypoxia increases glutamate, which causes an ion flux and cell swelling following activation of N-methyl-D-aspartate receptors. This could occur in hypoxia associated with DKA as well (11).

Ketones and Acidosis: Initiation of the Proinflammatory Cytokine Cascade. As mentioned previously, several authors have tried to relate the severity of acidosis in DKA to the risk of CE and/or the degree of altered mental status (82–85). It is interesting to note, however, that one patient who was not acidotic was reported to have developed CE (107). Acetoacetate and β -hydroxybutyrate, in addition to having an osmotic effect (96) and stimulating the sodium/proton exchanger (74), are proinflammatory agents that affect the endothelial cells of the blood-brain barrier (50, 55, 108). Acetoacetate increases intracellular calcium concentration in endothelial cells, causing vasoconstriction (108). β -hydroxybutyrate increases vascular permeability factor, also leading to an increase in endothelial cell intracellular calcium concentration (108). Hyperglycemia itself promotes inflammation via an increased glucose metabolite (109) and reactive oxygen species (110). There is increasingly convincing evidence of the proinflammatory state in patients with DKA at the time of admission and an increase in levels at the expected time of onset of symptomatic CE. C-reactive protein, which induces adhesion molecule expression in endothelial cells and stimulates macrophage production of cytokines at sites of inflammation, both of which lead to an increase in endothelial cell permeability (vasogenic edema), is increased in humans with DKA without signs of infection (111). Interleukin-6, interleukin- 1β , and tumor necrosis factor- α levels were also elevated before, during, and following treatment of DKA. Interleukin-10 is elevated as well, increasing at the time of symptomatic CE (112). Pathologic examination of human brain tissue also has provided evidence of activation of the complement system (113).

MRI studies that report findings consistent with vasogenic edema due to a

perturbation of the endothelial cells of the blood-brain barrier are also consistent with an increase in proinflammatory cytokines (14, 31, 44, 50, 56, 57). A generalized inflammatory response to metabolic factors, such as hyperglycemia and acidosis, is also consistent with the clinical findings of pulmonary edema concomitantly found in some patients with CE (114–119).

Aquaporin Channels. Aquaporin channels in glial cells transport water from the extracellular to the intracellular space and demonstrate a compensatory increase in expression in a streptozotocin DKA rat model (81). In an aquaporin-4 knockout or depletion model in mice, there is reduced CE formation in both water intoxication and ischemic stroke (120). Abnormalities in the number of functioning aquaporin channels in brain glial cells on either a genetic or an acquired basis as the result of metabolic stresses could account for the development of CE in certain individuals.

Diagnosis

Presentation. Although the phenomenon of CEDKA was first identified in 1936 in adults (2), since being reported by Fitzgerald et al. (121) and Young and Bradley (122) in children, CEDKA has generally been regarded as a disease of young children (1, 11, 123–125). Muir et al. (1) proposed a useful system of major and minor diagnostic criteria for the clinical diagnosis of CEDKA (Table 1). The minor criteria are frequently present in patients who do not develop symptomatic CE. The authors indicate that signs that occur before treatment should not be considered in the diagnosis of CE, although symptomatic CE may occur before treatment. Some authors indicate that the first signs of CE may be respiratory arrest and fixed dilated pupils (11), although this is disputed by those who believe that careful monitoring will reveal signs and symptoms before catastrophic collapse (1, 54).

Even though symptomatic CE does occur in adults (2, 16, 126–145), it is generally considered a disease of young children. Ninety-five percent of patients are <20 yrs of age, and 33% are <5 yrs of age. Sixty-seven percent are patients with new-onset DKA (11). The reasons for this finding are unknown. Potential explanations include a relatively greater brain volume for overall body size, more rapid changes in plasma osmolality, lack of sex

Table 1. Bedside evaluation of neurological state of children with diabetic ketoacidosis

Diagnostic criteria ^a
Abnormal motor or verbal response to pain
Decorticate or decerebrate posture
Cranial nerve palsy (especially III, IV, and VI)
Abnormal neurogenic respiratory pattern (e.g. grunting, tachypnea, Cheyne-Stokes respiration, apneusis)
Major criteria
Altered mentation/fluctuating level of consciousness
Sustained heart rate deceleration (decline more than 20 beats per minute) not attributable to improved intravascular volume or sleep state
Age-inappropriate incontinence
Minor criteria
Vomiting
Headache
Lethargy or being not easily aroused from sleep
Diastolic blood pressure >90 mm Hg
Age <5 years

^aSigns that occur before treatment should not be considered in the diagnosis of cerebral edema.

Reproduced with permission from Muir AB et al (1).

steroids, less developed mechanisms of brain cell volume regulation, differences in taurine or other osmolyte metabolism, differences in blood-brain barrier efficiency, and more rapid metabolism and water turnover in children (11, 84, 91). However, the exact reason for the apparently more frequent occurrence in children than adults is unknown. It is also possible that subclinical CE is common in both children and adults but that symptomatic CE is more common in children. It is also possible that the true incidence of CE in adults in DKA is underappreciated.

Subclinical vs. Symptomatic Cerebral Edema. In 1985, Krane et al. (146) reported a series of CT scans in six children 11–14 yrs of age with DKA who were all asymptomatic for CE; the authors compared scans taken early in the course after treatment was started with scans repeated at discharge, and all showed evidence of CE. The authors concluded that subclinical swelling was common in children with DKA after treatment began. This conclusion had been reached previously in a study that used head ultrasonography to examine 18 children and adults in DKA who were asymptomatic for CE (132).

In a study of eight patients ages 4–15 yrs in DKA (one with new-onset DKA)

who were admitted in a coma, Smedman et al. (147) performed CT scans 10 hrs after therapy began and repeated the scan after full recovery (all patients). The authors found evidence of CE in only two of eight patients and concluded that asymptomatic CE does not occur commonly. Glaser et al. (148), using MRI brain scans in 41 children during treatment and after recovery, found the lateral ventricles to be significantly smaller during DKA treatment than after recovery, and those with smaller ventricles during treatment were most likely to have mental status changes, which were seen in half the patients. These data suggest that there is a continuum of clinically relevant CE from modest to severe (149). However, Muir et al. (1), as well as others, emphasized that many symptomatic patients with CE have a normal early CT scan that subsequently becomes abnormal later in the course and that CEDKA is not a CT scan but a clinical diagnosis.

Early imaging studies as well as reports of other risk factors, such as fluid, insulin, and sodium bicarbonate administration, emphasized the occurrence of both subclinical and symptomatic CE after initiation of treatment for DKA, implicating the treatments themselves as risk factors in its development (32). However, Hoffman et al. (53) and Steinhart and Hoffman (55), as well as others (5, 9, 49–52, 54), documented occurrences of subclinical and symptomatic CEDKA, including even a death (51), before onset of therapy. Hoffman et al. (53) studied nine consecutive patients with DKA aged 6–17 yrs who were asymptomatic for CE. The investigators performed CT scans before treatment began, 6–8 hrs after starting treatment, and 7 days later. All patients had evidence of CE, and it was present before treatment was initiated.

Incidence. The incidence of symptomatic CEDKA is thought to be approximately <1% and is remarkably similar in several studies, both prospective and retrospective, and in different countries (5, 9, 10, 150, 151). Edge et al. (151), conducting a population-based study from 1995 to 1998 in the United Kingdom, found an incidence of 7.1 in 1,000 from a total of 2,941 episodes of DKA in children <16 yrs of age. The authors noted that CEDKA was more common in new-onset disease, with an incidence of 11.9 in 1,000 in patients with new-onset DKA but only 4.3 in 1,000 in those with known disease. This may relate to later detection in new-onset patients.

In the United States, Glaser et al. (5) conducted a retrospective study of 6,977 episodes of DKA from 1982 to 1997 and found an incidence of 0.9% (61 of 6,977). In Canada, Lawrence et al. (9) conducted a prospective study of cases of CEDKA from 1999 to 2001 and found 13 cases of CE from a total of 1,960 cases of DKA, for an incidence of 0.51%. Some of the difficulty in determining the incidence of subclinical CEDKA by clinical means alone has to do, in part, with the different definitions used for diagnosis (1, 5, 6, 125, 148, 149).

Differential Diagnosis. Certainly not all patients with DKA and altered mental status have symptomatic CE. As indicated earlier, patients with minor criteria alone may not be diagnosable by clinical means. Other intracranial pathology may exist in as many as 10% to 20% of symptomatic patients (11, 54, 123, 137, 152–159). Processes to consider include hypoglycemia, nonketotic hyperosmolality, drug ingestions, infection (e.g., meningitis, encephalitis), hemorrhage (spontaneous or traumatic), thrombosis, emboli, stroke, infarction, extrapontine myelinolysis, obstructive hydrocephalus, and trauma. Some clinicians remind us that after initiation of treatment for mental status changes, central nervous system imaging is advisable in all patients, especially those who do not clearly improve, because of these other causes of altered mental status (11, 26, 160, 161).

Although less frequent than central nervous system pathology and CE, other causes of morbidity are found in pediatric patients with DKA. These include hyperkalemia and hypokalemia with arrhythmia, sepsis, pneumonia, pulmonary edema, acute respiratory distress syndrome, alveolar rupture with free air, and rhabdomyolysis (123).

Therapy of Cerebral Edema in Diabetic Ketoacidosis

Here I review the currently proposed recommendations for treating symptomatic CEDKA. These recommendations are based in large part on individual case reports and opinions.

Early Signs of Cerebral Edema. Several authors (1, 54, 162) emphasize that careful neurologic and cardiorespiratory monitoring of patients often can lead to recognition of early warning signs and symptoms of symptomatic CE and therefore early treatment and better outcome. These signs and symptoms are presented

in Table 1. In the report by Muir et al. (1), at least two warning signs of neurologic compromise or increased ICP were documented in the records of 10 of 12 patients before a catastrophic event. General overall recommendations for treatment are prescribed by several authors, suggesting good or better results with early aggressive intervention (123, 163–165, 167, 168). Specific recommendations for use of mannitol, hypertonic saline, intubation and hyperventilation, steroids, and ICP monitoring follow.

Mannitol. Roberts et al. (169) described 11 patients with severe DKA with cerebral complications, nine of whom were treated early with mannitol and had complete recovery. Mannitol may improve patients' outcomes by osmotic diuresis and by decreasing blood viscosity, thereby improving cerebral blood flow and oxygen delivery. Rosenbloom (54) also indicated a role for early treatment with mannitol. Of 23 patients treated before respiratory arrest, 13 survived with independent function and three were severely disabled. Of 46 patients not treated before respiratory arrest, only three survived and were normal. Two patients were not treated and did not experience respiratory arrest. Shabbir et al. (170) and Franklin et al. (171) also reported good results with mannitol.

Hypertonic Saline. Some authors have reported using hypertonic saline instead of mannitol to treat CEDKA with some success (172, 173). The primary advantages proposed for hypertonic saline are that it prevents or mitigates hyponatremia and prevents hypovolemia associated with osmotic diuresis produced by mannitol, thus aggravating cerebral ischemia. Hypertonic saline also provides similar rheologic effects as mannitol, decreasing blood viscosity and improving cerebral blood flow.

Intubation and Hyperventilation. Intubation and ventilation are indicated to protect the airway in comatose patients and provide ventilation in apneic individuals (54, 166). Although some authors suggest using hyperventilation to treat CE, this has been identified as a risk factor for a worse outcome (8,163). Conversely, when patients are spontaneously hyperventilating to lower $Paco_2$ levels, ventilating them at normal levels may be detrimental as well (75). Patients with symptomatic CE who are intubated should probably be ventilated to $Paco_2$ levels existing at the time intubation is performed (75–80).

Steroids. Only one author (129, 174) has attributed a successful outcome to use of steroids in a patient with CE. Steroids certainly will complicate the management of hyperglycemia, and most authors do not recommend their use (123, 163).

Intracranial Pressure Monitoring. Two reports (175, 176) advocate the use of ICP monitoring to manage a patient with CEDKA. Others report use of ICP monitors (151).

Prognosis of Symptomatic Cerebral Edema in Diabetic Ketoacidosis

In considering the relationship of treatment to outcome in symptomatic CE, it is interesting to note that some reports indicate a good outcome without specific treatment (54, 151, 177). In examining 31 patients with symptomatic CE, Edge et al. (151) reported that four of 34 patients received no specific treatment; eight of 34 died, and 26 of 34 survived. Seventeen of 26 survivors were normal, nine of 26 had persistent morbidity. Morbidities in the nine included motor deficits in eight visual impairment in six, memory loss in six, and seizures in two. As indicated previously, Rosenbloom (54) reported on 69 patients with a mortality rate of 64%; most of the patients who died were not treated until experiencing respiratory arrest. Mahoney et al. (83) reported on nine patients with symptomatic CE, five of whom died. Two of four survivors were intact and two were impaired. Glaser et al. (5) reported on 61 patients with symptomatic CE. Thirty-five of the 61 recovered without sequelae; 13 had permanent neurologic sequelae and 13 died. Lawrence et al. (9) studied

13 patients with symptomatic CE; three (23%) died and two (15%) recovered with neurologic impairment. Long-term morbidity (178) and complete or partial hypopituitarism (153, 179, 180) have been reported in other survivors.

Therapy of DKA: Prevention of CE

Certainly the best way to prevent CEDKA is to prevent DKA (93–95). Once DKA occurs, however, clinicians can refer to several excellent guidelines for management (59, 123, 124, 161, 167, 181–186) as well as excellent general guidelines for fluid management in pediatric patients (186, 187). These guidelines show a change over time from recommendations for bolus doses to continuous insulin infusions, more cautious fluid administration, and avoidance of sodium bicarbonate, although some recent recommendations vary (188), and variation in practice has been documented to be considerable (189, 190). I next discuss recommendations specifically addressing fluid, insulin, and sodium bicarbonate administration and correction of electrolyte abnormalities as they relate to prevention of CE. These recommendations are made in the absence of definitive evidence of the association of specific disease or treatment risk factors for CE or an understanding of specific underlying mechanisms.

Fluid Administration. It seems prudent to avoid excessive amounts of fluid, fluid given too rapidly, and use of hypotonic fluid (33, 90, 91, 123, 184, 191–193). Most authors do not recommend that a bolus of fluid be given unless there is evidence of cardiovascular compromise as demonstrated by extreme tachycardia,

hypotension, cold extremities, and/or anuria. The degree of dehydration in these patients is frequently overestimated (167, 194). If a bolus is given for hemodynamic instability, do not continue to use boluses once circulatory stability is demonstrated. Use isotonic (0.9%) sodium chloride solution for boluses and to correct deficits. Maintenance fluids can be given with 0.45% sodium chloride solutions. Deficits should be estimated at 5% to 7% of weight unless shock is present, in which case assume 10% to 15% loss of body weight. Replace fluid deficits at a rate of 1/48 per hour, evenly over 48 hrs. After any initial bolus, fluids can be administered at a rate rarely in excess of 1.5–2.0 times the usual daily requirement (Table 2). Urinary losses should not be added to the calculation of replacement fluids. This recommendation has only class E support, and many clinicians do recommend replacing urinary losses. Do not decrease serum osmolality rapidly (191). Many clinicians decrease osmolality at a rate ≤ 1.5 –2.0 mOsm/hr.

Insulin Administration. Bolus insulin administration is no longer used in pediatric patients (123). Administer insulin at a rate of 0.1 unit/kg/hr (123, 184). This is a class A evidence recommendation of the European and American Endocrinology Societies based on prospective, controlled, clinical trials. Many authors and clinicians (especially intensivists) recommend 0.05 units/hr. If blood glucose decreases at a rate of < 50 mg/dL/hr or if the patient fails to start to correct in 2–4 hrs, increase the insulin to 0.15 units/kg/hr. If the blood glucose decreases to < 350 mg/dL or > 100 mg/dL/hr, add glucose in a ratio of 4–5 g/unit of insulin. As a guideline, many clinicians do not let the glucose decrease > 50 –100 mg/hr. Due to

Table 2. Water and salt replacement in diabetic ketoacidosis^a

- Water and salt deficits must be replaced. IV or oral fluids that may have been given before the child presents for treatment and prior to assessment should be factored into calculation of deficit and repair (A).
- Initial IV fluid administration and, if needed, volume expansion should begin immediately with an isotonic solution (0.9% saline or balanced salt solutions such as Ringer's lactate). The volume and rate of administration depend on circulatory status, and where it is clinically indicated, the volume is typically 10 to 20 mL/kg over 1 to 2 hours, repeated if necessary (E).
- Use crystalloid (C).
- Subsequent fluid management should be with a solution with a tonicity $\geq 0.45\%$ saline (C):
This can be achieved by administering 0.9% saline or balanced salt solution (Ringer's lactate or 0.45% saline with added potassium) (E).
Rate of IV fluid should be calculated to rehydrate evenly over at least 48 hours (E).
- In addition to clinical assessment of dehydration, calculation of effective osmolality may be valuable to guide fluid and electrolyte therapy (E).
- The severity of dehydration may be difficult to determine and can be overestimated, infuse fluid each day at a rate rarely in excess of 1.5 to 2 times the usual daily requirement based on age, weight, or body surface area. Urinary losses should not be added to the calculation of replacement fluids (E).

^aLetters in parenthesis are classes of evidence A through E; IV, intravenous. See reference 123, appendix. Reproduced with permission from Dunger et al (123).

the frequent large decrease in blood glucose seen with initial fluid therapy, some clinicians do not start insulin until after initial fluid boluses are given when necessary.

Sodium Bicarbonate Administration. It is difficult to justify a complete prohibition on use of sodium bicarbonate (10, 11, 123). One may give 0.5–1.0 mEq/kg over 30–60 mins in children with severe circulatory compromise and high risk of decompensation due to profound acidosis. There is debate as to whether this is necessary (64, 73), since acidosis may not cause myocardial depression in these patients. Various definitions of severe acidosis are used, including pH <7.1, <7.0, and <6.9. Although it is not completely convincing that sodium bicarbonate is dangerous, there is no evidence that it is beneficial in these patients.

Correction of Electrolyte Abnormalities. It is not known whether failure of sodium to increase during treatment or a decrease in serum sodium causes CE or is a consequence of already existing cerebral injury (7, 58). In either case, use isotonic (0.9%) sodium chloride solution for bolus and initial therapy to correct fluid deficits until serum sodium is in normal range.

Patients are usually potassium and phosphate depleted (123, 184). Potassium depletion is in the range of 3–6 mmol/kg, and insulin administration will accentuate this by drawing potassium into cells. Proper potassium replacement may help prevent arrhythmias. Phosphate deficits are in the range of 0.5–2.5 mmol/kg and need to be addressed as well (184). Adequate phosphate levels may help preserve energy availability.

CONCLUSIONS

The causes and mechanisms of CEDKA are unknown. CE may have as much to do with individual biological variance as with the severity of the underlying metabolic derangement at the time of presentation or any one or combination of risk factors associated with treatment of DKA. Although I have presented treatment recommendations, attempting to consider proposed risk factors and mechanisms of CE, I cannot be dogmatic about these recommendations in the absence of better evidence. CE still occurs when these treatment guidelines are followed, and well-documented cases representing the unpredictability of this phenomenon remind us of how poorly it

is understood (23, 92). It is best to be extremely vigilant in monitoring patients; most will have been ill for many days by the time they present, and therefore careful, slow correction of their metabolic derangement is prudent.

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