

Cerebral edema in children with diabetic ketoacidosis

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INTRODUCTION — Cerebral edema is an uncommon but potentially devastating consequence of diabetic ketoacidosis (DKA). It is far more common among children with DKA than among adults. Young children and those with newly diagnosed diabetes are at highest risk. Symptoms typically emerge during treatment for DKA, but may be present prior to initiation of therapy.

The pathophysiology, diagnosis, and treatment of cerebral edema in children with diabetic ketoacidosis will be discussed here. The diagnosis and treatment of diabetic ketoacidosis in children is discussed separately. (See "Clinical features and diagnosis of diabetic ketoacidosis in children" and "Treatment and complications of diabetic ketoacidosis in children".)

INCIDENCE — Clinically significant cerebral edema occurs in approximately 1 percent of episodes of diabetic ketoacidosis in children and has a mortality rate of 20 to 90 percent; 50 to 80 percent of diabetes-related deaths are caused by cerebral edema [1-3]. Overall mortality rates for diabetic ketoacidosis (DKA) in children range from 0.15 to 0.51 percent in national population studies in Canada, the United Kingdom, and the United States [4-7]. Other causes of death from DKA include aspiration pneumonia, multiple organ failure, gastric perforation, and traumatic hydrothorax [5].

Subclinical brain swelling, as detected by ventricular narrowing on a CT scan, has been reported in the majority of children with DKA in some studies [8,9], while others reported much smaller proportions [10]. All of these studies were limited by small numbers and lack of appropriate control groups.

In a study of 41 children with DKA, the intercaudate width of the frontal horns of the lateral ventricles was measured by magnetic resonance imaging (MRI) [11]. The lateral ventricles were significantly smaller in patients during treatment for DKA than after recovery (mean width 9.3 ± 0.3 versus 10.2 ± 0.3 mm, respectively). Fifty-six percent of the children had ventricular narrowing during treatment, and these children were more likely to have mental status changes

than those without narrowed ventricles (Glasgow coma scale scores below 15 occurred in 12 of 22 with ventricular narrowing, versus 4 of 19 without).

Despite the lack of a control group, these findings suggest that cerebral swelling occurs commonly in children with DKA. However, it remains unclear whether subclinical brain swelling noted in this study is a precursor to clinically significant cerebral edema and if so, what factors determine progression. Similar changes in mental status have been reported among children with other causes of acidosis, so it is difficult to determine whether the observed mental status changes in this study are due to the cerebral edema or to the underlying acidosis [11,12].

PATHOPHYSIOLOGY — The cause of cerebral edema in DKA is not fully understood, and the only definite way to prevent it is to avoid DKA [13]. Although in the past decade multiple studies have increased our understanding, they all have substantial limitations, including the retrospective nature of the studies, the heterogeneity in the management of each of the patients, and their small sample sizes. These limitations are inevitable given the rare and unpredictable nature of cerebral edema in DKA. Nonetheless, such studies provide general principles for management that are considered safe and are summarized by several consensus statements [1,14].

Cerebral edema may be present before treatment has begun, but more commonly occurs 4 to 12 hours after the initiation of therapy [5,8,9,14-17]. Thus, therapy may exacerbate but not initiate the pathologic process(es) leading to cerebral edema.

Numerous factors have been implicated in the pathophysiology of DKA-related cerebral edema, but none has been proven. Ischemic, vasogenic, osmotic, or cytotoxic processes have been proposed, as discussed below. It is possible that DKA-related cerebral edema is due to a combination of two or more of these factors. In addition, other metabolic and inflammatory factors, such as hyperglycemia-induced increase in blood-brain barrier permeability, and the generation of new solutes within the brain by hyperglycemia itself and by insulin therapy may contribute to its pathogenesis [18-21]. (See "Manifestations of hyponatremia and hypernatremia".)

Proposed mechanisms

Ischemia/cytotoxic edema — Studies utilizing proton MR spectroscopy have shown a decrease of N-acetylaspartate (NAA), a marker of neuronal function or viability, in children with DKA in several areas of the brain, including the basal ganglia and occipital and peri-aqueductal gray matter. These observations suggest, therefore, that cerebral ischemia may play a role in the pathophysiology of DKA-related cerebral edema [22], a hypothesis further supported by several observations including:

Increased lactate production in the basal ganglia in children with DKA [23]. Breakdown in blood-brain barrier, decrease in neuronal density, and increases in pro-inflammatory mediators and cytotoxic markers in fatal cases of cerebral edema [24-26].

Vasogenic edema — The term "vasogenic" edema describes a process in which primary damage to the cerebral vascular endothelium results in increased blood-brain barrier permeability or a disturbance in autoregulation, which permits abnormal diffusion of intravascular fluids into the cerebral tissues. A variety of observations suggest that this mechanism is an important contributor to cerebral edema in the setting of DKA: Studies using MRI imaging demonstrate water diffusion into cerebral tissues during treatment for DKA [27,28] while others suggest an abnormality in blood-brain barrier permeability [29]. Normal or increased cerebral blood flow and oxygenation has been observed despite hypocapnia, suggesting defective vascular autoregulation [29,30]. Together, these studies support the idea of a vasogenic mechanism for fluid shifts into the brain during treatment for DKA.

These studies are small and examine children undergoing treatment for DKA, but without clinical evidence of cerebral edema. It remains unclear whether these observations also describe the mechanisms underlying the more dramatic fluid shifts that occur in children who develop clinically significant cerebral edema.

Osmotic edema as a consequence of fluid therapy — If the extracellular compartment is at a lower osmolality than the intracellular compartment, osmotic pressure promotes water movement into the intracellular compartment. During DKA, the combination of insulin and fluid repletion lowers the serum glucose and plasma osmolality, promoting osmotic water movement into the brain [18-20].

This mechanism provides a logical explanation for the development of cerebral edema as a result of the osmotic changes that occur during treatment for DKA. However, these fluid shifts happen in all patients with DKA, yet only approximately 1 percent of patients develop clinically significant cerebral edema. Proponents of this hypothesis advocate the use of "physiologic management" of DKA that includes a planned replacement of fluid and electrolyte deficits over 48 hours and strongly argue that such an approach reduces the risk of cerebral edema. In one report of patients managed by this method, fluid replacement actually occurred much faster than planned (fluid replacement was complete around 12 hours of therapy rather than 48 hours as planned) [31]. The proportion of patients treated for cerebral edema was not lower as compared with other series, perhaps because patients were identified and treated at earlier stages of symptomatology. Remarkably, there was zero mortality and morbidity from cerebral edema in this series. These observations suggest that early identification of cerebral edema and aggressive intervention with mannitol can help eliminate mortality and morbidity, but do not independently support the efficacy of "physiologic management".

Risk factors — Several risk factors for developing cerebral edema in children with DKA have been identified [1,14,17]. Some of these risk factors may merely reflect a longer period of symptoms prior to diagnosis with a greater likelihood of presenting with severe DKA.

Younger children [2,5,32]

Children with newly diagnosed diabetes [2,3]

Failure of the serum sodium to rise as predicted following insulin therapy and fluid repletion, indicating a greater fall in plasma osmolality [18,33-36]; in one report, for example, the effective plasma osmolality fell significantly more in patients who developed cerebral edema compared to those who did not (9 versus 1 to 2 mOsmol/kg at four hours) [33]

Increased blood urea nitrogen at presentation of DKA, which may represent a greater degree of hypovolemia [2,7]

The severity of acidosis at presentation [7,19,37], although acidosis was not important in an animal model [20]

The use of bicarbonate therapy for correction of the acidosis in DKA [2,38]

After adjusting for the severity of acidosis, a lower initial partial pressure of arterial carbon dioxide [2,39]

Studies conflict in their conclusions about whether the rate of fluid or insulin administration is associated with an increased risk of cerebral edema, perhaps because of the difficulty of designing adequate controls for this type of study. Several studies have suggested that rapid correction of dehydration using hypotonic fluids increases intracranial pressure in patients with DKA [33,37,39,40]. Similarly, the administration of greater amounts of insulin during the initial phases of treatment may increase the risk of cerebral edema [33,37]. However, a larger and well-designed study did not identify either rate of fluid or insulin administration as a risk factor [2]. Given the lack of definite answers, we suggest cautious use of fluids and insulin to minimize any possible risks.

In our current practice, we avoid the use of bicarbonate and aim for an appropriate rise in serum sodium concentration as the glucose concentration falls. We try to correct the effective circulating volume gradually. In the initial stages, we restore glomerular filtration rate with isotonic fluid, and avoid hypotonic solutions.

SIGNS AND SYMPTOMS — The presentation of cerebral edema varies but the onset of headache is usually the earliest symptom. Altered level of consciousness, sustained heart rate deceleration, or age-inappropriate incontinence are important early signs of impending neurologic collapse [1]. These symptoms often occur prior to notable changes in head computed tomography. Frequent monitoring at the bedside for early symptoms of cerebral edema may identify these children sufficiently early for intervention to prevent brain damage [41]. (See 'Treatment' below and "Elevated intracranial pressure (ICP) in children".)

Bedside evaluation — The following criteria may be helpful in identifying children who may progress to severe, life-threatening cerebral edema [1,41]. The presence of any of the symptoms listed below should raise suspicion for the possibility of cerebral edema. Children with severe DKA can have an altered mental status that is due to other factors including the degree of dehydration, metabolic derangements, and sleep deprivation. Nonetheless, clinicians should maintain a high level of suspicion for evidence of cerebral edema and intervene promptly if the diagnosis is suspected. By the time the diagnostic criteria develop, cerebral edema is already in an advanced stage, and morbidity and mortality are high [3,14,17,41].

Cerebral edema is diagnosed if any of the diagnostic criteria listed below is present. Cerebral edema is also likely if two major criteria OR one major and two minor criteria are present (table 1).

Diagnostic criteria

Abnormal motor or verbal response to pain

Decorticate or decerebrate posture

Cranial nerve palsy (especially III, IV, and VI)

Abnormal neurogenic respiratory pattern (eg, 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 not easily aroused from sleep

Diastolic blood pressure >90 mmHg

Age <5 years

TREATMENT — An essential part of therapy in DKA is careful monitoring for changes in mental or neurologic status that would permit early identification and therapy of cerebral edema. As soon as cerebral edema is suspected, treatment should be initiated. The 2004 ESPE/LWPES consensus statement recommends the following [14,17]:

The rate of fluid administration should be reduced.

Mannitol should be given at 0.25 to 1.0 g/kg intravenously over 20 minutes. The mannitol dose may be repeated in two hours, if there is no initial response. This recommendation is based upon the suggested beneficial effect of mannitol in case reports [42-44]. In a retrospective study of 61 patients with cerebral edema, mannitol did not appear to have either a beneficial or detrimental effect [45]. However, the majority of patients in this study presented with symptoms

suggesting severe cerebral edema, so these results should not be interpreted to suggest that mannitol is ineffective in earlier stages of cerebral edema. 3 percent saline (5 to 10 mL/kg over 30 minutes), has been used as an alternative hypertonic agent, but clinical experience is limited [46,47]. Intubation and mechanical ventilation may be required. However, hyperventilation should be avoided and has been associated with a poor outcome in patients whose pCO₂ was driven below 22 mmHg [45]. Aggressive hyperventilation (beyond the baseline hyperventilation present in most patients with DKA) may decrease cerebral blood flow enough to cause cerebral ischemia and actually increase the extent of brain injury in any form of cerebral edema. (See "Elevated intracranial pressure (ICP) in children", section on 'Hyperventilation'.)

OUTCOME — The mortality rate among children with DKA who develop cerebral edema is approximately 20 to 25 percent; among survivors, approximately 15 to 35 percent have permanent sequelae [1,3,45].

Risk factors for death or survival in a vegetative state were identified in a retrospective multicenter study of 61 children [45]:

Elevated blood urea nitrogen at the time of initial presentation.

Intubation with hyperventilation with a pCO₂ of less than 22 mmHg.

Severe neurologic compromise at presentation. All patients who either died or survived in a persistent vegetative state presented with a Glasgow coma score ≤7 (score of 6 to 7 includes an abnormal or absent purposeful response to pain scores) (table 2).

No prospective studies have been performed to determine if early identification of children with cerebral edema can reduce morbidity and mortality. Nonetheless, given the poor outcomes cited above, we recommend that concerted efforts be made to identify and treat children with cerebral edema.

SUMMARY AND RECOMMENDATIONS

Cerebral edema is responsible for 50 to 80 percent of deaths related to diabetic ketoacidosis in children. Among children with DKA who develop cerebral edema, the mortality rate is 20 to 25 percent, and 15 to 35 percent of survivors have permanent neurologic sequelae. (See 'Introduction' above.)

Children who are younger, newly diagnosed with DKA, or who present with elevated BUN, more profound acidosis, or neurologic symptoms are at greatest risk for cerebral edema. (See 'Risk factors' above.)

We recommend careful evaluation and monitoring for signs and symptoms of cerebral edema in all children undergoing treatment for DKA (Grade 1C). Specific signs of increased intracranial pressure and changes detectable by head computed tomography often occur too late for effective intervention. Therefore, we recommend monitoring for symptoms that may occur earlier in the development of cerebral edema. These symptoms include headache, recurrent

vomiting, and altered level of consciousness, as outlined in the bedside evaluation protocol (table 1). (See 'Signs and symptoms' above.) Changes detectable by head computed tomography occur late in the development of cerebral edema. Therefore, the decision to treat should be based on clinical evaluation. Imaging may be useful to exclude other causes of neurological deterioration, but should not delay treatment. If cerebral edema is suspected, we recommend beginning treatment promptly by reducing the rate of fluid administration (Grade 1C) and administering mannitol (0.25 to 1.0 g/kg) (Grade 2C) or hypertonic (3 percent) saline. Mechanical hyperventilation is generally not recommended. Treatment options have not been rigorously studied, but prompt and aggressive treatment is appropriate given the high morbidity and mortality of cerebral edema. (See 'Treatment' above.) Use of UpToDate is subject to the Subscription and License Agreement.

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