Review Article

Cerebral Edema in Diabetic Ketoacidosis

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Cerebral edema is the most important complication of diabetic ketoacidosis in children. It has a high mortality rate of 20 to 90% in different series. Twenty to 40% of survivors suffer from neurologic sequelae. The pathogenetic mechanisms are still controversial and the risk factors which are thought to predict its occurrence do not consistently correlate with cerebral edema in various studies. Prevention and recognition of early warning signs, such as decreased arousal, lethargy after initial improvement, headache, vomiting, relative bradycardia and relative hypertension, are crucial. Therapeutic guidelines to prevent cerebral edema in diabetic ketoacidosis include slow rehydration over about 48 hours, avoidance of hypotonicity and of unnecessary alkali therapy. Early recognition of cerebral edema and prompt institution of hypertonic therapy with mannitol may prevent permanent neurological sequelae.

Key words: *Cerebral edema, Diabetic ketoacidosis.*

Diabetic ketoacidosis (DKA) occurs in 25-40% of children with newly diagnosed type 1 diabetes mellitus (DM)(1). It may occur later also in association with infection, other stress or non-compliance with treatment. Cerebral edema is the most important complication of DKA as it is associated with a high mortality rate of 20 to 90 % in various series(2-6). Of the survivors, 20 to 40 % suffer from serious and permanent neurologic disability including motor deficits, visual impairment, seizure disorder, learning disability and speech disturbance(2,5). Clinically, apparent cerebral edema occurs in approximately 1% of episodes of DKA; asymptomatic swelling occurs more frequently(4,7). Cerebral edema complicating DKA is a pediatric problem and is almost unknown in adults(2). The reason for the predisposition of children to cerebral edema as well as the pathogenetic mechanisms of this complication are unclear even now, 70 years after its initial description(8). Presented here are the current ideas regarding the mechanisms, possible prevention, early recognition and treatment of cerebral edema in DKA.

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Presentation and diagnosis

Cerebral edema typically occurs 4-12 hours after treatment is activated(6,9). However, it may develop any time during treatment for DKA and can even be present before treatment has begun(7,10-13). Cerebral edema is primarily a clinical diagnosis and should be suspected when there is an unexpected deterioration in neurological status after initial improvement or persistence of a comatose state without an obvious cause. Warning signs include lethargy, decrease in arousal, headache, vomiting, bradycardia and hypertension (*Table I*)(2). Neurological deterioration may be rapid, with seizures, incontinence, pupillary changes and respiratory arrest. Progression may be so rapid that papilledema may not be found. The signs progress as brainstem

TABLE I–*Warning Signs of Cerebral Edema in Diabetic Ketoacidosis*

Early signs	Late signs
Headache	Seizures
Vomiting	Incontinence
Decreased arousal, lethargy	Pupillary changes
Relative bradycardia	Upgoing plantars
Relative hypertension	Respiratory arrest

herniation occurs. Rosenbloom reported postmortem studies on 24 of his series of 69 patients(2). Cerebral edema was universal and brain stem herniation was present in almost all. Either CT scan or postmortem studies were available in 58 of his 69 patients. Based on the results of these modalities, he speculated that about 10% of episodes of clinical cerebral edema are due to localized basilar edema, and another 8 to 10% are as a result of infection, thrombosis or hemorrhage.

Once clinical symptoms other than lethargy and behavioral changes occur, mortality is high (>70%), with only 7-14% of the patients recovering without permanent morbidity(14). Rapid improvement in neurological status in response to intravenous administration of 3% sodium chloride or hypertonic mannitol further confirms the presumptive diagnosis of early cerebral edema. Making and acting on a clinical diagnosis should take precedence over performing a CT scan because the latter might delay the implementation of emergency therapy(2). In fact, confirmatory changes of cerebral edema on CT scan studies frequently do not keep pace with the clinical course, and they might not be sensitive enough to detect cerebral edema. Moreover, care might suffer when patient is transported to an area of the hospital where continuous monitoring may not be possible.

Demography

Various demographic factors have been associated with an increased risk of cerebral edema in some studies but not in others. Two population based studies of demographic factors associated with cerebral edema in DKA have been reported in recent years(5,13). In a prospective record of all cases of DKA in the UK over a 3-year period between 1995 and 1998, Edge, *et al.* reported 34 cases of well documented cerebral edema from among 2940 episodes of DKA (0.68% or 6.8 per 1000 cases)(5). A further 26 children with unexplained deterioration in consciousness and 2 deaths in children suspected to have had cerebral edema before admission to hospital were not included in this statistic. The Canadian prospective population based study also reported a similar frequency of 5.1 per 1000 cases of DKA (13 episodes of cerebral edema among 1960 episodes of DKA)(13). Expectedly, far higher frequencies have been reported from centers which cater to the sickest children, for example 13.2% in a report from a pediatric intensive care unit of a tertiary care hospital in India(15). Edge, *et al*. reported higher frequency of cerebral edema in new onset type 1 DM (11.9 per 1000 cases) compared to children with known DM (3.8 per 1000 cases)(5). This association was also reported by the Canadian study(13) and other non-population based reports(2,3), and on univariate (but not multivariate) analysis in a multicentre study from North America(6). Association with younger age group has been noted in the largest description of cases of cerebral edema(2) though not in the recent prospective population based reports(5,13). Bellos, *et al*. have reported an association with longer duration of symptoms before treatment of diabetes(3).

Pathogenesis

Cerebral edema has been hypo-

thesized to result from either one of two broad pathogenetic mechanisms or a combination of both: (*a*) breakdown of the endothelium blood-brain barrier leading to interstitial brain edema *(vasogenic edema)* or (*b*) from swelling of astrocytes as a result of altered intracellular osmotic balance or dysfunctional cellular membrane (*cytotoxic edema*). The main pathogenetic mechanisms invoked for these are detailed below(16) .

Vasogenic edema

1. *Hypoxia induced damage of the blood brain barrier:* Acidosis and dehydration decrease CNS perfusion and induce hypoxia which in turn damages the blood brain barrier. On the background of a damaged less restrictive blood brain barrier, as soon as rehydration is begun and the plasma osmolality falls, there occurs movement of water from the lower osmolal plasma to the higher osmolal interstitial fluid of the brain, thus increasing intracranial pressure.
2. A bolus of saline during initial therapy increases the *hydrostatic pressure in the capillaries* and forces water out into the interstitium more rapidly.

Cytotoxic edema

1. *The formation of osmolytes within the brain cell:* During the period of prolonged hyperglycemia prior to the institution of treatment for diabetes or DKA, the plasma and interstitial osmolality rise. The osmolality within the cells is kept up by the formation of osmolytes (formerly called idiogenic osmoles), which are now known to be molecules such as taurine and myoinositol(17). When intravenous fluid therapy is started, even normal saline is hypotonic compared to the plasma osmolality of the patient. Thus, the plasma osmolality is suddenly lowered, whereas due to slow movement of osmolytes intracellular osmolality remains high, forcing water from the low osmolal region (plasma) into the high osmolal region (the astrocyte).
2. *Activation of the brain Na^+- H^+ exchanger by insulin.* This exchanger, which facilitates Na^+ movement into the cell and H+ movement outside the cell, is normally inactive in the brain as movement of these ions in the desired direction is brought about by their concentration gradient itself. However, a bolus of insulin could activate the exchanger(18,19). During acidosis, the high intracellular H^+ ion concentration coupled with an active exchanger drives H^+ outside the cell and Na^+ into it. The H^+ ions were originally bound to cell proteins and did not contribute to solute load in the cell. In contrast, the Na^+ ions which have moved into the cell do increase the osmolality. The resulting high intracellular osmotic load draws water into the cell, causing cell swelling.

Attractive though these proposed mechanisms are in theory, not all have been proved by clinical observation or animal experiments. Clinical observations supporting the above theories are:

1. Children's brains have greater oxygen consumption than adults and hence are more vulnerable to hypoxia. Cerebral edema complicating DKA is almost limited to children(2).
2. The duration of hyperglycemia before treatment of DKA and blood urea at admission, both surrogates for the level of dehydration, correlate with incidence of cerebral edema(3,6,13). The degree of hypocapnia, which decreases cerebral perfusion by causing vasoconstriction,

similarly correlates with incidence of cerebral edema(6,20). Glaser, *et al.* reported lower partial pressure of carbon dioxide in 61 DKA cases with cerebral edema in comparison with not only 184 random DKA controls but also 174 cases matched for venous pH. The association remained significant on multivariate analysis(6).

3. Alkali therapy, which can cause paradoxical CNS acidosis, was shown in an experimental study to produce cerebral hypoxia in dogs(21). In the clinical study by Glaser, *et al.*, the use of bicarbonate gave a relative risk 4.2 (95% CI 1.5-12.1, $p < 0.008$) for the development of cerebral edema.

4. A delayed or inadequate rise in corrected serum sodium as glucose levels fall during therapy of DKA (giving rise to lower plasma osmolality) has been correlated with occurrence of cerebral edema in a large number of studies(6,22-25).

5. Glaser, *et al.,* in a study of diffusion and perfusion weighted MRI of the brain in 14 children with DKA, reported expansion of the extracellular space and changes consistent with vasogenic edema, in the earliest (subclinical) stages of edema(16).

Clinical and experimental observations which do not support the above theories:

1. If the fall in osmolality plays an important role, the rate and type of intravenous fluid administration, blood glucose at onset and the rate of fall of blood glucose should correlate with occurrence of cerebral edema. Though Durr, *et al.*(26) showed blood glucose at onset and the rate of fall of blood glucose and osmolality with treatment to correlate positively with occurrence and progression of asymptomatic cerebral edema as seen by CT scan, this has not been shown to be the case in most studies of symptomatic cerebral edema(2,3,6,20,27,28). Secondly, though the use of hypoosmolal (0.45%) saline was found to be associated with cerebral edema by Harris, *et al.*(23), the subsequent prospective study by the same group(29), where serum sodium levels were guarded very carefully, still had 6 of 149 cases of DKA requiring mannitol. Furthermore, 5 of these 6 cases showed appropriately rising trend of serum sodium.

2. Severity of acidosis was found to correlate significantly in the study of asymptomatic cerebral edema by Durr, *et al*. as described above(26) as well as the Canadian population based study(13) but not in other clinical symptomatic cerebral edema reports(2,6).

3. Concomitant with the activation of the Na^+-H^+ exchanger, there occur other complex alterations such as activation of other pumps which induce a loss of other anions and cations from the brain cell.

Several authors have attempted to reconcile these apparently disparate and conflicting observations and hypotheses by highlighting the fact that different mechanisms may be relevant at different times during the course of DKA and the evolution of cerebral edema. The absence of animal models of DKA which mimic human cerebral edema is an impediment. With the availability of non-invasive tools which allow in vivo metabolic studies, such as PET scanning and MR spectroscopy, it is hoped new information will be gained on the earliest changes leading up to cerebral edema in DKA.

Prevention

The pediatric endocrine and diabetes

associations of Europe and North America have recently formulated joint consensus guidelines for the treatment of DKA(30,31). Those aspects which might bear relevance to cerebral edema are presented here.

1. Dehydration in DKA is a hyperosmotic state that calls for slow repair, optimally over 48 hours. Some children, with very high serum osmolality, may require rehydration to be done even slower than over 48 hours.
2. Use of a fluid that has sodium and chloride or sodium, chloride and bicarbonate in physiological amounts (*i.e.*, isotonic with normal extracellular fluid) is recommended. Later in therapy, the sodium chloride concentration may be 0.45- 0.9%.
3. If the patient is not hypotensive, rehydration is best achieved evenly over 48 hours. In other words, the maintenance requirement for 48 hours is added to the estimated deficit, and the total is delivered over 48 hours. If the patient is hypotensive, isotonic saline is given rapidly at 10 to 20 mL/kg/hour until stability is restored, then the rate is immediately slowed down to give the remainder volume over 48 hours. No more than 50 mL/kg is recommended in the first 4 hours of rehydration. Ongoing urine loss volume is not added as it is offset by water of metabolism.
4. In estimating the patients' deficit, we must not assume a 10-15% body weight loss unless shock is present. The losses, especially in older children, are usually close to 5-7% of body weight. It is useful to remember to account for the bolus of I/V fluid the child may have received at another health care facility before the current admission, to avoid rapid hydration.
5. Insulin is given by the low dose infusion of 0.1 units/kg/hr (or the same dose I/M every hour if I/V access is not available) and continued I/V till there is closure of anion-gap and/or pH is greater than 7.3 and bicarbonate greater than 15 mmol/L. The initial bolus I/V dose is not recommended for children. Hyperglycemia should be reduced gradually by 50 to 100 mg/hr. Switching to a dextrose containing solution early, at a blood glucose of about 250 mg/dL helps to avoid rapid fluctuations of osmolality. Maximum reduction in osmolality should be 3 mOsm/kg water/hr.
6. The American Diabetes Association has recommended that the use of bicarbonate should be reserved for those patients with an arterial pH of <7.0 after one hour of rehydration if they have circulatory compromise as a result of the acidosis. (The European Society for Pediatric Endocrinology/ Lawson Wilkins Pediatric Endocrine Society consensus statement on diabetic ketoacidosis has been even more conservative and has recommended the same at a pH below 6.9). The other indication may be symptomatic hyper-kalemia. If at all required, it is given in a dose of approximately 2 mEq/kg, added to a sodium chloride solution so as to make the final concentration of sodium 150 mEq/L, infused over 2 hours. Furthermore, all low bicarbonate is not always indicative of ketoacidosis. During successful therapy, the clinician should expect hyperchloremic non-anion gap acidosis. If the anion gap gradually normalizes during therapy, a subsequent period of hyperchloremic non-anion gap acidosis is of no clinical concern, except in the presence of acute renal failure. This also stresses the need for monitoring anion gap during therapy.

Key Messages

- Cerebral edema associated with diabetic ketoacidosis is primarily a clinical diagnosis. Early warning signs include drowsiness after initial improvement, headache, vomiting, relative bradycardia and relative hypertension.
- Slow rehydration is advocated in diabetic ketoacidosis, as is avoidance of hypotonicity and unnecessary alkali therapy, to minimize risk for cerebral edema.
- Intravenous mannitol 0.25-1.0 g/kg is to be given as soon as the diagnosis of cerebral edema is suspected.
- Cerebral edema has a high mortality rate of 20 to 90 %. Of the survivors, 20 to 40% suffer serious neurologic disability.

Treatment of cerebral edema

Treatment should be initiated as soon as the condition is suspected, without waiting to make any diagnostic investigation. Early recognition is aided by close monitoring of every child with DKA, and a high threshold of suspicion for symptoms and signs such as headache, vomiting, diminished arousability, lethargy, relative bradycardia (there may just be a decrease of pulse rate from say 90 beats to 70 beats per min) and relative hypertension. Cerebral edema can occur before the onset of therapy for DKA. Therefore, one must be alert to this possibility even at initial admission.

1. Rate of fluid administration should be decreased.
2. Intravenous mannitol 0.25-1.0 g/kg should be given over 20 minutes. It can be repeated in 2 hours if there is no initial response, and may need to be repeated later even if there is a good response.
3. Hypertonic saline (3 %) 5-10 mL/kg over 30 minutes is an alternative to mannitol(32).
4. Intubation and ventilation may be necessary. However, aggressive hyper-ventilation has been associated with poor outcome in one retrospective study of DKA related cerebral edema(33).

Outcome

In Rosenbloom's analysis of 69 patients, more than 50% of patients treated for cerebral edema before the occurrence of respiratory arrest survived completely normal or had neurogical impairment which did not preclude independent existence(2). In contrast, only 6.5% of those treated after respiratory arrest survived with independent existence. Though other factors which were not presented in the analysis may have been operative in those with favourable outcome, this description belies the popularly held belief that mortality is universal in cerebral edema, and argues for vigorous efforts to prevent DKA, prevent cerebral edema, recognize and treat it early.

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