

## REVIEW

## Cerebral oedema in childhood diabetic ketoacidosis: Is treatment a factor?

T B Brown

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Cerebral oedema (CO) is the most dreaded complication of diabetic ketoacidosis (DKA) in children. Despite advances in many areas of the management of DKA, the mortality from CO has remained constant for decades. This rare disorder, complicating about 1% of cases of DKA in children, is lethal in 20% to 50% of victims. Since it was first described in 1936, much effort has gone into the search for a cause for this condition, but CO in childhood DKA remains a mysterious illness. Researchers have suggested that the treatment for DKA may be causally related to the development of CO. Others have disputed this claim, and both camps cite evidence to support their point of view. This article reviews the literature pertinent to the question: Is the treatment of DKA in children responsible for the development of CO?

during treatment are an ominous sign for potentially impending CO.

This article reviews the literature pertinent to the question: Is the treatment of DKA in children responsible for the development of CO? Brief investigation demonstrated that the evidence pertinent to the question is limited, so before the formal search the decision was made to include as evidence all trials, case-control studies, case series, and cohort studies. Case reports, letters, comments, editorials, and reviews were excluded as evidence. The National Library of Medicine's PubMed database was searched using the keywords "cerebral edema and diabetic ketoacidosis" and limited to the English language and human subjects. This search yielded 133 references. Eighty five of these were excluded by title alone, and 11 were excluded based upon a review of the abstract. Twelve articles were excluded after careful reading. Twenty five articles were selected for inclusion.<sup>2 3 5 6 8–28</sup> The references cited in each of the included articles were reviewed, and four additional articles were identified.<sup>1 4 7 29</sup> This review covers 21 articles (see table 1) that can be cited as evidence.<sup>3–6 9–11 13–15 18 21–23 29</sup> The remaining references are used for discussion and include information on death rates,<sup>1 2</sup> several case reports,<sup>5 16 17</sup> a hypothesis proposal,<sup>12</sup> and treatment guidelines.<sup>19 20</sup> The author is unaware of any other studies relevant to the topic; all studies identified in the search are included in this review except the above noted exclusions. In this way, the relevant evidence is included and discussed.

Cerebral oedema (CO) is the most dreaded complication of diabetic ketoacidosis (DKA) in children. Despite advances in many areas of the management of DKA, the mortality from CO has remained fairly constant for the past six decades.<sup>1–4</sup> Mortality estimates vary widely, but some authors suggest this disorder is lethal in about 20% to 50% of victims.<sup>5 6</sup> Fortunately, it is a rare occurrence, complicating about 1% of cases of DKA in children.<sup>5</sup> Since it was first described in 1936, much effort has gone into the search for a cause for this condition.<sup>7</sup> Despite these attempts, CO in childhood DKA remains a mysterious illness. It is unpredictable, sporadic, and deadly.

Researchers have suggested that the treatment for DKA may be causally related to the development of CO.<sup>3 4 8–12</sup> The theory suggests that overzealous insulin use or hydration with excess free water administration to children with DKA cause a dramatic dysequilibrium between the osmolality of the serum and that of the brain. A fluid shift along this osmolar gradient is then responsible for CO. According to this theory, there are osmotically active substances in brain cells that prevent dehydration during acute hyperglycaemia. When the serum glucose is rapidly lowered these substances remain in the brain cells, and an intracellular osmotic gradient is created that results in CO. Proponents of this theory also feel that excess secretion of anti-diuretic hormone may occur and that rapidly falling serum osmolality and serum sodium concentrations that decline or remain constant

Several authors have sought relations between the treatment of DKA and the development of CO. The theory of causality is supported by several studies that relate the decline in serum glucose and downward trends in serum sodium seen in some cases of CO to rate and tonicity of fluid administration.<sup>3 4 8 10 11 13 29</sup> Many of these studies suffer from methodological flaws that render them inconclusive.

Duck and Wyatt reviewed 42 cases of DKA associated CO and found an inverse relation between rate of fluid administration and time to herniation.<sup>10</sup> From these data, they conclude that rapid fluid administration may be associated with CO, and they recommend limiting the rate of fluid hydration. However, there are no controls, making it difficult to conclude that

Correspondence to:  
Dr T B Brown, UCLA  
Emergency Medicine  
Center, 23630 Latana  
Court, Valencia, CA  
91355, USA;  
tbransonbrown@attbi.com

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**Abbreviations:** CO, cerebral oedema; DKA, diabetic ketoacidosis

**Table 1** Summary of available evidence relating treatment of diabetic ketoacidosis to development of cerebral oedema

Paper	Number	Methods	Conclusions
Harris <i>et al</i> , 1990 <sup>3</sup>	219 DKA cases. 58 DKA cases	Retrospective chart review Prospective interventional study	Sodium trend may correlate with DKA risk
Glaser <i>et al</i> 2001 <sup>5</sup>	6977 DKA cases. 61 CO cases	Retrospective case-control	CO risk not related to fluids or insulin
Rosenbloom 1990 <sup>4</sup>	69 CO cases	Case series	CO risk not related to treatment
Mahoney <i>et al</i> 1999 <sup>9</sup>	195 DKA cases. 9 CO cases	Retrospective chart review	Fluid administration associated with CO risk
Vlcek 1986 <sup>4</sup>	5 CO cases. 15 controls	Retrospective case-control	CO risk related to fluids
Duck <i>et al</i> 1976 <sup>9</sup>	4 CO cases	Case series	Treatments may be related to CO risk
Duck, Wyatt 1988 <sup>10</sup>	42 CO cases	Case series	CO risk may be related to fluids
Harris, Fiordalisi 1994 <sup>11</sup>	231 DKA cases. Zero CO cases	Prospective study	Conservative treatment may reduce risk for CO
Bello, Sotos 1990 <sup>13</sup>	11 CO cases. 20 controls	Retrospective case-control	CO in DKA may have osmolar cause
Durr <i>et al</i> 1992 <sup>29</sup>	7 DKA cases. Zero clinical CO cases	CT evidence of CO correlated to change in osmolality	CO may exist before treatment, but may worsen with aggressive treatment
Krane <i>et al</i> 1995 <sup>14</sup>	6 DKA cases. Zero clinical CO cases	Observational report of serial CT scans during treatment	Subclinical cases of CO may be common during treatment
Clements <i>et al</i> 1971 <sup>15</sup>	5 DKA cases. Zero clinical CO cases	CSF pressure monitored continuously during treatment	Increased CSF pressure may be common during treatment
Rosenbloom <i>et al</i> 1980 <sup>18</sup>	17 CO cases	Case series	CO risk not related to treatment
Hoffman <i>et al</i> 1988 <sup>21</sup>	9 DKA cases. Zero CO cases	Observational report of serial CT scans during treatment	Cerebral swelling is usually present before treatment
Mel, Werther 1995 <sup>22</sup>	6 CO of 3134 DKA. 6 CO of 3373 DKA	Retrospective comparison of two different treatment cohorts	CO risk not related to treatment
Edge, Dunger 1994 <sup>23</sup>	25 management protocols	Protocols evaluated for outcome differences	Aggressive treatment may increase CO risk
Felner, White 2001 <sup>24</sup>	520 DKA cases. 0.3–0.5% CO rate	Retrospective comparison of two different treatment cohorts	CO risk similar in the two protocols
Fein <i>et al</i> 1982 <sup>25</sup>	18 DKA cases. Zero CO cases	Serial echoencephalograms during treatment	CO risk may be related to treatment
Smedman <i>et al</i> 1997 <sup>26</sup>	8 DKA cases	Observational report of serial CT scans during treatment	Subclinical CO does not occur regularly during DKA treatment
Hale <i>et al</i> 1997 <sup>27</sup>	4 CE cases. 10 controls	Retrospective case-control	CO may be related to declining sodium
Edge <i>et al</i> 2001 <sup>28</sup>	2940 DKA cases. 34 CO cases	Large descriptive study producing risk estimates	CO is an important complication of DKA

the unfortunate victims of CO received hydration at a different rate than other patients. Furthermore, it is probable that patients who are more acidemic, hypocapnic, and dehydrated are at greater risk for catastrophic outcomes, and these are the very patients who may require more aggressive hydration because of the severity of their illness. The authors also noted a trend of decreasing serum sodium concentration in the study group, which they suggest as a risk factor for impending CO.

Bello and Sotos compared retrospective data on 11 cases of DKA associated CO with 20 random ketoacidotic controls.<sup>13</sup> The decrease in serum osmolality in patients with CO was related to a 53% decrease in serum glucose and a 38% decrease in serum sodium. In controls, 99% of the decrease was related to the fall in serum glucose. Again, declining serum sodium seemed to be an ominous sign. They found no relations between CO and fluid rate, rate of glucose fall, or pH. Administration of NaCl, NaHCO<sub>3</sub>, or insulin did not correlate with development of CO. Only the decrease of serum osmolality and the duration of symptoms before treatment predicted its development.

Harris *et al* studied 219 cases of DKA in which they reported 20 complicated episodes.<sup>3</sup> Seven of these were classified as major complications, defined as acute deterioration in vital signs or neurological status. Of the seven, only two were identified by chart review, while the remaining five were identified by the recollection of the authors. Three had confirmed CO, and the remaining four had suspected CO. The authors found that serum sodium failed to rise in response to hydration in 18 of 20 (90%) complicated patients but only 99 of 182 (54%) controls. They concluded that a downward

serum sodium trend in response to hydration is a strong predictor of complications attributable to brain swelling. In part two of this study, 58 episodes of DKA were prospectively evaluated to determine if a treatment regimen individualised to each patient could prevent neurological compromise. The goal was to increase serum sodium concentration while serum glucose levels declined. The protocol demonstrated 95% success in meeting this objective, and there were no major complications. However, the sample size limits the validity of the conclusions. As DKA associated CO has an incidence of 1%, a study this size is unlikely to capture any cases of CO regardless of the treatment used.

Many of these studies are uncontrolled, and most are retrospective. The few prospective studies that exist and attempt to recommend therapeutic strategies have not included any cases of CO.<sup>3–11</sup> The investigators are forced to use as markers for potentially impending CO controversial trends and associations developed from previous retrospective studies, such as rate of change of serum osmolality and the trend of the serum sodium concentration. These markers have not been consistently related to CO. As DKA associated CO has an incidence of about 1%, any realistic attempt to prospectively evaluate the effect of treatment must have many hundreds of patients. The largest prospective trial to date contains only 231 episodes of DKA, and there were no cases of CO.<sup>11</sup> The authors conclude that their therapeutic regimen limiting initial rehydration can protect against life threatening increases in intracranial pressure and brain herniation. However, they treated six patients with mannitol for clinical manifestations worrisome for CO. That represents 3% of the study group, an incidence of CO higher than that

reported in other series. As mannitol may have efficacy in the treatment of CO, its use calls into question the safety of the regimen used in this study.<sup>6, 13</sup>

A recent review in the United Kingdom by Edge and Dunger attempted to correlate DKA treatment protocols with rates of CE.<sup>23</sup> CO appeared more frequently in those centres with protocols that suggested more rapid initial hydration, higher rates of maintenance fluid, and treatment with more hypotonic fluid. Unfortunately, no attempt was made to discover if patients were actually treated according to the suggested protocols. Thus comparison of the differing protocols is problematic. Furthermore, the cases of CO were based solely upon the recollection of physicians from the various centres, not upon more rigorous criteria that would ensure all cases were included.

Several authors have shown that subclinical CO exists in many cases of DKA. Krane *et al* found CT scans compatible with brain swelling in each of six children evaluated during treatment of DKA.<sup>14</sup> None of these patients developed clinically significant CO. Hoffman *et al* examined serial cranial CT scans of nine children with DKA.<sup>21</sup> Pretreatment scans showed findings consistent with brain swelling, but there were no differences between the pretreatment scans and scans done six to eight hours into treatment. Again, there were no cases of CO. Durr *et al* found that six of seven patients had CT evidence for brain swelling on admission, before treatment was started.<sup>29</sup> In this study serial CT scans were done during treatment, and a trend linking progression of brain oedema and declining plasma osmolality was identified. Only one patient developed signs and symptoms worrisome for CO, and this patient responded promptly to mannitol. Smedman *et al* failed to find any radiological evidence of significant brain swelling in eight children treated for DKA.<sup>26</sup> Clements *et al* have demonstrated rising cerebrospinal fluid pressure as serum osmolality decreases during treatment for DKA, but again in the absence of any case of clinical CO.<sup>15</sup> Fein *et al* reported radiological evidence of brain swelling during treatment for DKA, and correlated the apparent swelling to decreasing serum colloid oncotic pressure; but there were no cases of CO.<sup>25</sup> These studies are alike in their lack of significant cerebral abnormality, and they cannot be used to infer any relation between treatment and clinical CO. These results suggest that many patients with DKA develop subclinical brain swelling during treatment and even before treatment begins, but no conclusive evidence has demonstrated a link between treatment and the development of DKA associated CO. In fact, CO occasionally occurs in association with DKA before any possible treatment effect.<sup>16, 17</sup>

One report by Rosenbloom *et al* reviewed 17 cases of DKA associated CO.<sup>18</sup> The authors found no role for rate of fluid or electrolyte administration, or for rate of blood glucose correction. Two episodes of CO had only oral rehydration. Another study by Rosenbloom reviewed 69 cases of DKA associated CE. This retrospective analysis did not implicate rate of hydration, tonicity of administered fluid, rate of correction of glucose, or use of bicarbonate in the development of CO. Mel and Werther reported a 20 year retrospective experience during which two large groups of children were rehydrated according to two differing protocols. One involved rapid correction of dehydration over six hours, and the other used a longer 24 hour period. There was no difference in the rate of CO between the treatment groups.<sup>22</sup> A small retrospective study by Hale *et al* compared four cases of CO with 10 matched controls, but found no difference between the volume and sodium content of fluid administered to the two groups.<sup>27</sup> Although the authors suggest a trend of declining serum sodium may be an ominous sign, they conclude that

“DKA itself, rather than its treatment, causes CE [cerebral edema].”

Felner and White evaluated the difference in outcomes resulting from a change in the treatment protocol for children with DKA at their institution.<sup>24</sup> Both protocols suggested initial fluid bolus therapy for states of hypoperfusion. Bolus treatment had been followed by replacement of a fluid deficit calculated as 1.5 times maintenance fluids plus fluids based on the child's weight and percentage dehydration. This was done over 36 hours, half in the first 12 hours and half in the next 24 hours. The new protocol suggested a weight based fluid regimen delivered at 2.5 times the maintenance rate, regardless of the percentage dehydration. The new protocol was also designed to use fluids that are less hypotonic (0.75 normal saline versus 0.5 normal saline), and to allow more rigorous control over the delivery of sodium and glucose to patients. The new protocol was successful in more rapidly correcting acidosis than the old, and it was found to be more cost effective. However, although patients treated under the new protocol received less total fluid, the rates of CO were no different between the treatment groups.

Edge *et al* conducted a survey in which they attempted to identify every case of CO that occurred during DKA over a two year period in England, Scotland, and Wales.<sup>28</sup> They determined the overall risk of CO was seven per 1000 cases of DKA, a rate strikingly similar to rates reported in the United States. The authors point out that the fluid management for DKA differs between the UK and the US. In the UK, colloid solutions have been used for the initial resuscitation, whereas US practitioners have used normal or even half normal saline. Similarly, practitioners in the UK have used isotonic saline for subsequent hydration, but in the US hypotonic saline has been more common. “Thus the similar risk of cerebral edema in the UK and the USA suggests that the type of fluid regimen used in the treatment of DKA may have only a limited impact on cerebral edema risk.”

A recent study by Glaser *et al* retrospectively examined 6977 cases of childhood DKA.<sup>5</sup> They identified 61 cases of CO in this group. Each case of CO was paired with six controls. Three controls were randomly assigned from among the initial pool of 6977 patients, and three controls were matched according to age, onset of diabetes, venous pH at presentation, and serum glucose concentration at presentation. This review found no relation between CO and rates of fluid, sodium, or insulin administration. There was no correlation between CO and initial serum glucose concentration or the rate of change of serum glucose concentration. Of therapeutic factors analysed, only treatment with bicarbonate was associated with CO, and this association is confounded by the reality that only the most toxic, acidemic children are considered for bicarbonate treatment. The children who developed CO had higher initial serum urea nitrogen concentrations and lower initial partial pressures of arterial carbon dioxide, which implies that they were more dehydrated and acidemic—in other words, they were sicker. This study is large, methodologically sound, and strongly refutes previous reports attempting to link the development of CO with the treatment of children in DKA.

Considering the inconclusive nature of the current literature, no treatment strategies can be definitively recommended. Some studies have suggested that vigorous hydration leading to rapid changes in osmolality may be associated with CO, but they have insufficient methodology to suggest a causal relation. Other large trials do not show any relation between hydration treatment and CO. Variation from proposed rehydration protocols<sup>19, 20</sup> must be left to the discretion of the treating physician, but rate of dehydration, level of acidosis, serum osmolality, and serum glucose concentration should all be taken into account. Unless a

large prospective trial is performed with enough power to identify differences in outcomes after treatment regimens of children with DKA, definitive therapeutic recommendations will be impossible. Because DKA associated CO is a rare condition, each treatment arm of such a study would require thousands of patients. A large, multicentre trial over many years would be needed. Although feasible and ethical, such a study would require herculean effort. Based on the current state of the literature, the idea that treatment for DKA results in CO must be considered an unsubstantiated myth.

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