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The etiology of cerebral edema in DKA managed patients

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Abstract

Background: Cerebral edema is the most frequent and serious complication of diabetic ketoacidosis in children. Signs and symptoms of clinically apparent CE usually become evident within the first 12 hours of treatment, but can occur before treatment has been initiated,14-18 or, rarely, as late as 24 to 48 hours after starting treatment. Overt Cerebral edema complicating diabetic ketoacidosis is fatal in 20- 30% of individuals and, overall, Cerebral edema accounts for approximately 50-90% of childhood diabetes-related deaths.

Aim of study: to discuss the latest theoties in the origin of cerebral edema among pediatric diabetic patients.

Methods: We reviewed literature from online platforms such as, google scholar, PubMed, American journal of pediatrics. We searched about the keywords (pediatric cerebral edema, mechanism, etiology, and pathogenesis), we collected eight researches and articles, and we analyzed their results and outcomes.

Results: the general outcomes from the 8 researches was that the etiology of cerebral edema in diabetics is multifactorial and very complex and a lot of hypotheses was made and supported by evidences from human and animal models.

Conclusion: The exact mechanism still not well understood but there is some advances in this field and we should wait for results soon.

Keywords: pediatrics, cerebral edema, etiology

Introduction

Diabetic ketoacidosis (DKA) occurs in 25% to 40% of children with new-onset type 1 diabetes mellitus and can recur in children with established diabetes during episodes of intercurrent illness or if insulin injections are omitted. With appropriate therapy, the majority of children recover from DKA uneventfully. In approximately 1% to 5% of cases, however, the DKA episode is complicated by symptomatic cerebral edema (1).

Cerebral edema is the most frequent and serious complication of diabetic ketoacidosis (DKA) in children. Clinically apparent cerebral edema occurs in approximately 1% of childhood DKA and is associated with high mortality and neurological morbidity. The pathogenesis of the cerebral edema, however, is not understood; investigators have attributed it to cellular swelling as a result of rapid osmolar changes occurring during intravenous infusions. Several studies, however, have shown no relationship to the volume or sodium content of the infusion nor any association with the rate of change in serum glucose concentration. This suggests that other factors may be important in the pathophysiology of DKA-related cerebral edema (2).

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 (3).

Signs and symptoms of clinically apparent CE usually become evident within the first 12 hours of treatment, but can occur before treatment has been initiated,14-18 or, rarely, as late as 24 to 48 hours after starting treatment. Overt CE complicating DKA is fatal in 20-30% of individuals and, overall, CE accounts for approximately 50-90% of childhood diabetes-related deaths (4). Between 10% and 35% of survivors of CE have residual disabilities ranging from mild neurological impairment to a vegetative state. The finding of both acute and long-term impairment of cognition and memory function in children with a history of DKA indicates that cerebral injury occurs even without evidence of overt CE (5).

Aim of study

To discuss the latest theories and hypotheses in the etiology cerebral edema caused by DKA.

Methods

We reviewed literature from online platforms such as, google scholar, PubMed, American journal of pediatrics. We searched about the keywords (pediatric cerebral edema, mechanism, etiology, pathogenesis) and we collected 8 researches and articles that their dates ranged from (2005 to 2021) and we analyzed their results and outcomes. we chosed them based on their outcomes, their difference in the explanations for the etiology CE and the used techniques used in the studies (murine, radiological studies with CT scan, laboratory methods and literature review).

Results

It has been postulated that cytotoxic injury plays a prominent role early in the development of CE, before starting treatment for DKA, and may contribute to its propagation during treatment. This theory is supported by studies in rats, which have demonstrated significant reductions in the apparent diffusion coefficient (ADC) during conditions simulating untreated DKA, suggesting restricted diffusion of water molecules and indicating cellular swelling (9) To determine whether the effects of hypocapnia on the brain are altered during hyperglycemia or ketosis, they induced hypocapnia (pCO_2 20 ± 3 mmHg) via mechanical ventilation in three groups of juvenile rats: 25 controls, 22 hyperglycemic rats (serum glucose 451± 78 mg/dL) and 15 ketotic rats (beta-hydroxy butyrate 3.0 ± 1.0 mmol/L). they used magnetic resonance imaging to measure cerebral blood flow (CBF) and apparent diffusion coefficient (ADC) values in these groups and in 17 ventilated rats with normal pCO_2 (40±3 mmHg). In a subset (n=35), after 2 hrs of hypocapnia, pCO_2 levels were normalized (40±3 mmHg) and ADC and CBF measurements repeated. Declines in CBF with hypocapnia occurred in all groups. Normalization of pCO_2 after hypocapnia resulted in striatal hyperemia. These effects were not substantially altered by hyperglycemia or ketosis, however, declines in ADC during hypocapnia were greater during both hyperglycemia and ketosis (9).

Several studies have found that patients with DKA who develop CE present with more severe hyperglycemia than those without overt CE. CE was observed in 22 (8.6%) of the 256 subjects included in the study. One of these patients (5%) had a fatal outcome and two patients (9%) survived

with neurological consequences. CO was significantly associated with severe DKA: lower initial venous pH ($p < 0.001$) and bicarbonate ($p < 0.001$), higher initial blood glucose ($p < 0.01$), urea level ($p < 0.05$) and baseline serum osmolality ($p < 0.05$). During the treatment of DKA, low serum phosphate level was found to be significantly associated with CO ($p < 0.05$). they also found significant dependence between the development of CO and the initiation of treatment for DKA in another facility before hospitalization in our hospital ($p < 0.05$), bicarbonate application ($p < 0.001$), (10).

Vasogenic edema refers to damage of the cerebral vascular endothelial layer resulting in increased blood brain barrier dysfunction, allowing abnormal diffusion of fluid into the central nervous system. This has been suggested from observational data based on MRI showing abnormal diffusion of fluid into the brain Magnetic resonance imaging (MRI)—diffusion-weighted imaging (DWI) and T2 relaxometry (T2R)—were obtained in pediatric patients presenting with severe diabetic ketoacidosis (DKA) 6–12 hours after initial DKA treatment and stabilization and 96 hours after correction of DKA. T2 relaxometry was significantly increased during treatment in both white and gray matter, in comparison to the absolute T2R values 96 hours after correction of DKA. Classic intracellular cytotoxic edema could not be detected, based on the lack of a statistically significant decrease in ADC values (12).

A study (13) provides new information regarding cerebral edema during DKA. CBF was significantly reduced in DKA and was responsive to alterations in pCO_2. ADC values were reduced, consistent with cell swelling. The reduction in ADCs correlated with dehydration, as reflected in blood urea nitrogen concentrations. Bumetanide caused a rapid rise in ADCs of DKA rats without significantly changing CBF, while

saline/insulin caused a rapid rise in CBF and a gradual rise in ADCs. DKA rats treated with bumetanide plus saline/insulin showed a trend toward more rapid rise in cortical ADCs and a larger rise in striatal CBF than those observed with saline/insulin alone. They used diffusion MRI in the trial and it provided further evidence that subtle, asymptomatic cerebral edema may occur commonly in children during DKA treatment, although most patients had no symptoms or signs of cerebral edema (13).

Another mechanism commonly thought to result in edema is serum osmotic changes. This is based on the thought that osmolyte accumulation in the brain is due to the presence of the hyperosmolar state in DKA. Fluids resulting in a rapid decrease in the extracellular osmolar state would cause brain swelling .This is one of the predominant theories behind the recommendation for slow fluid and electrolyte replacement over 48 h, rather than in bolus form. Although this hypothesis is simple and easy to comprehend, data are lacking to support this (1). Another hypothesis holds that brain cells accumulate lactate, free fatty acids, and ketone bodies during the ketoacidotic state, resulting in intracellular acidosis. During treatment, systemic acidosis is corrected and insulin is administered, both of which are thought to activate the Na+/H+ exchanger in brain cells. Sodium is then thought to accumulate in brain cells, and swelling occurs on an osmotic basis as systemic osmolality decreases (14).

Acetoacetate and beta-hydroxybutyrate have been shown to stimulate Na-K-Cl cotransporter activity in rat astrocytes leading to intracellular accumulation of electrolytes and water. Several studies have also implicated the Na+/H+ exchanger in propagating neuronal injury in DKA. This exchanger is believed to be activated by cytoplasmic acidification from high concentrations of circulating organic acids and

elevated levels of vasopressin. In addition, cases had higher potassium and urea levels at baseline. Calculated osmolality and baseline glucose were not significantly different. After allowing for severity of acidosis, insulin administration in the first hour (OR 12.7 [1.41–114.5], p=0.02) and volume of fluid administered over the first 4 h (OR 6.55 [1.38–30.97], p=0.01) were associated with risk. Low baseline plasma sodium and an elevated p_aCO_2 also contributed to risk in the final regression model. Bicarbonate administration was not associated with increased risk of an event when corrected for acidosis. During DKA treatment, resolution of acidosis creates an outward chemical gradient for protons, which, together with a direct effect of insulin therapy, has been proposed to enhance the activity of this exchanger. These mechanisms are thought to promote influx of sodium and water into neurons leading to cellular swelling (15).

Another possible theory would be due rapid treatment of DKA, to either the overdose of insulin or the exaggerated hyperhydration of the effective intake of water in diabetic persons. One of these aspects, once applied, would lead to significant instability between plasma and cerebral osmolality. And this conception / opinion is based on the presence of some active substances at the cerebral level with role in preventing the installation of dehydration in case of hyperglycemia. When a rapid decline in blood sugar occurs, these osmoprotective substances persist in the nerve cell causing an intracellular osmotic gradient, which triggers edema. In addition to this mechanism, an eventual hypersecretion of antidiuretic hormone together with a rapid decrease in serum osmolality and a hypo / normonatremia during the treatment application may be an indication of the inevitable cerebral edema (17).

There are many evidence about the incidence of subclinical cerebral edema among diabetic patients. A study showed that narrowing of the lateral cerebral ventricles, indicating brain swelling, is evident on MRI in just over half of children being treated for DKA. In a study, they measured the intercaudate width of the frontal horns of the lateral ventricles using magnetic resonance imaging (MRI) in children with DKA during treatment and after recovery from the DKA episode. they determined the frequency of ventricular narrowing and compared clinical and biochemical data for children with and without ventricular narrowing. Forty-one children completed the study protocol. The lateral ventricles were significantly smaller during DKA treatment (mean width, 9.3 ± 0.3 vs. 10.2 ± 0.3 mm after recovery from DKA, $p < 0.001$). Children with ventricular narrowing during DKA treatment (22 children, 54%) were more likely to have mental status abnormalities than those without narrowing [12/22 vs. 4/19 with Glasgow Coma Scale (GCS) scores below 15 during therapy, $p = 0.03$]. Multiple logistic regression analysis revealed that a lower initial PCO_2 level was significantly associated with ventricular narrowing [odds ratio (OR) = 0.88, 95% confidence interval (95% CI)=0.78–0.99, p=0.047). (18).

Discussion

Cerebral edema (CE) is clinically apparent and life threatening in 0.5–1% of patients with DKA. Though the mortality of DKA is < 1%, CE accounts for a significant proportion of these deaths due to brain herniation, which can occur prior to initiation of treatment. Mortality ranges from 20–90%, with one-fourth of survivors suffering permanent neurologic deficits. However, CE may be asymptomatic or subtle, with minor mental status changes, which can appear in many cases of pediatric DKA. This severe complication presents most commonly within the first 7 h of treatment (66%), with 33% presenting 10–24 h after initiation of treatment in type 1 and type 2 diabetics (6). More important, however, the findings demonstrate that the ADC is increased, rather than decreased, during DKA treatment in most regions of the brain, likely indicating expansion of the extracellular space relative to the intracellular space. These findings are most consistent with a vasogenic mechanism of edema formation rather than osmotic cell swelling, which is associated with expansion of the intracellular space (2).

Subtle edema occurs in the majority of patients with DKA, as studies using neuroimaging (computed tomography [CT] or magnetic resonance imaging [MRI]) in children with DKA have demonstrated the presence of edema before treatment is initiated and during therapy. Patients who have abnormal mental status during treatment are likelier to

possess subtle CE, defined by cerebral ventricle narrowing, than those with normal neurologic status during treatment . Any abnormal neurologic assessment, including abnormal Glasgow Coma Scale score (GCS), is associated with higher frequency of MRI changes (7).

Many theories have been advanced to explain brain swelling in association with DKA, including over zealous rehydration with hypotonic intravenous fluids, the rapid reduction of blood glucose with insulin, activation of the Na/H transporter system, change in oncotic pressure, increased permeability of the blood brain barrier, and changes in cerebral blood flow (8). Other studies have also shown increases in lipid peroxidation and reductions in antioxidant vitamins C and E before and during treatment of DKA in children. In addition to cellular damage, lipid peroxidation and ROS have been implicated in endothelial membrane dysfunction at the level of the blood-brain barrier (BBB), suggesting concurrent vasogenic injury (11).

Several studies highlight the importance of the risk of developing cerebral edema in patients with uncontrolled glycaemic status for long periods of time. This risk factor has also been highlighted on experimental studies on murine and canine models. The theory is explained by the neural protection mechanism that develops as a result of consecutive hyperosmolarity of hyperglicemia. In order to maintain its normal cell volume in the contex of hyperosmolarity, the brain cell will synthesize active osmotic metabolic products such as taurine and myoinositol. These osmoli disappear from slow intracellular space in hours, or even days after correction of plasma osmolarity, which is explained by the fact that the downregulation of cotransporters can take up to 16 hours at the astrocytic level, as evidenced on murine models. These conditions promote the circulation of water from the extra

environment, into the intracellular environment, with consecutive cell edema (16).

Cerebral edema is serious complication and preventive methods should be carried on. If DKA could be prevented entirely, both at the time of initial diagnosis and in established diabetes, then cerebral edema could be avoided. A systematic review of factors associated with the presence of DKA at the diagnosis of type 1 diabetes reported that children presenting with DKA had symptoms for an average of 2 wk and up to a third had at least one medical consultation in the week before diagnosis. Delayed diagnosis of diabetes mellitus was associated with a threefold increase in DKA, so early recognition of symptoms of diabetes is the key to prevent DKA (19).

Until the causes of cerebral edema in DKA are understood more fully, guidelines for management of DKA can never be considered entirely safe. Therefore, prevention of DKA should be a major aim of services looking after children with diabetes. When children are undergoing treatment with DKA, this should be in a centre with facilities for constant monitoring of children's neurological, clinical, and biochemical state, so that at the first signs of raised intracranial pressure, osmotic treatments can be instituted rapidly to prevent long-term harm (20).

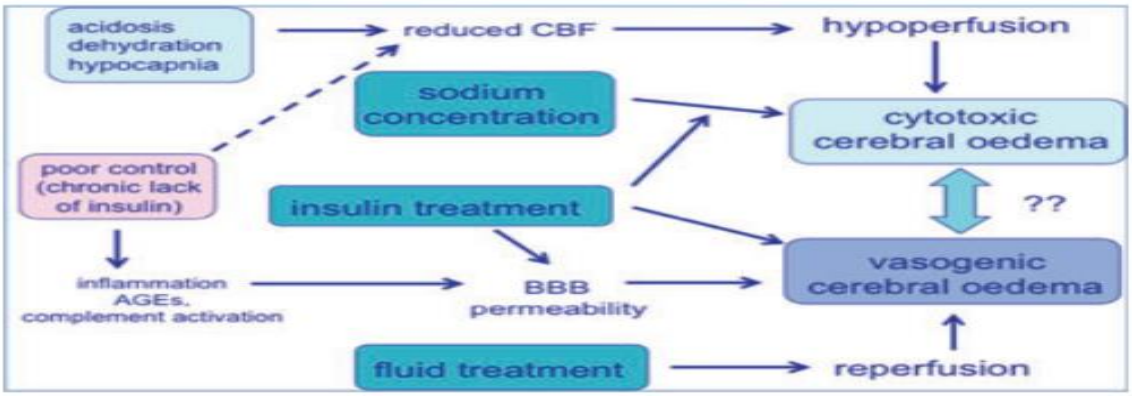

Figure 1. Some theories about the development of cerebral edema

Conclusion

Cerebral edema in diabetic ketoacidosis is very dangerous condition that affect the child physically and mentally. The exact mechanism still not well understood but there is some advances in this field and we should wait for results soon.

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