

Cerebral Oedema in Diabetic Ketoacidosis

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Abstract: *Cerebral oedema in diabetic ketoacidosis (CODKA) is a controversial subject both in medical and forensic practice as well as in the specialized literature, in the light of the non-homogeneous theories regarding the pathophysiological mechanisms. It would seem that the ground of CEDKA would be a combination/fusion of processes that affect both metabolic changes in diabetic ketoacidosis (DKA) and aggressive therapy to combat DKA. This article wants to underline the importance of knowing and deepening the pathophysiological mechanism that leads to the installation of cerebral oedema (CO) in DKA, focusing on the potential of the thanatogenerator mechanism.*

Keywords: *diabetic ketoacidosis; cerebral oedema; mechanism; death..*

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1. Introduction

Cerebral oedema in diabetic ketoacidosis (CODKA) is a controversial subject both in medical and forensic practice as well as in the specialized literature (Damian et al., 2019), in the light of the non-homogeneous theories regarding the pathophysiological mechanisms. It would seem that the ground of CEDKA would be a combination/fusion of processes that affect both metabolic changes in diabetic ketoacidosis (DKA) and aggressive therapy to combat DKA (Christopher et al., 2018).

It is known that DKA can be installed in people with diabetes, with high lethal potential. This can occur in both patients with type 1 diabetes and those with type 2 diabetes, being more common in young people with type 1 diabetes (Fayfman et al., 2017). This aspect derives from a multitude of metabolic imbalances, occurring in a diabetic patient, such as accumulation of toxic ketoacids, osmotic diuresis, sodium proton pump dysfunction and impaired intracellular potassium level (Christopher et al., 2018).

On the other hand, cerebral oedema (EO) represents a potentially fatal complication of diabetic ketoacidosis, installed secondary to metabolic abnormalities that occurred in DKA, being associated with a high mortality rate (Wachtel et al., 1991).

So far, the reason for installing Co in DKA is still not fully understood. The data published in the literature show the interest of the researchers for this important event that often leads to the death of the patient.

This article wants to underline the importance of knowing and deepening the pathophysiological mechanism (Gemene et al., 2018) that leads to the installation of cerebral oedema in DKA, focusing on the potential of the thanatogenerator mechanism.

2. General data on CO in DKA

EO represents the increase in brain volume following the abnormal accumulation of fluid, due to numerous biochemical, histochemical and biophysical factors. This phenomenon is considered as a very complex reaction, which is installed as a result of different etiologies, of cerebral or extracerebral nature. From an ehtipathogenic point of view, CO can be vasogenic - when the primary pathogenic factor leads to alteration of the vascular wall, with increased protein permeability and impairment of the blood-brain, or cytotoxic barrier - when the primary pathogenic factor leads

to alteration of the structure of the cerebral parenchyma, affecting the grey matter and / or the white matter, the blood-brain barrier remaining intact (Leestma, 2014).

In 1936 the first post-mortem CO in fatal DKA was described (Edge, 2000). Since then, various factors have been incriminated that could explain the EO installation in DKA, such as: hypoxia, ketone bodies, intracellular accumulation of osmolites, impairment of the sodium-proton pump, hyperosmolarity.

The main theories incriminated in the occurrence of CO in DKA are dependent on the time and type of initiation of DKA treatment. In this regard, there are studies that argue that the occurrence of CO in DKA is independent of the initiation of DKA treatment, namely that CO is installed before treatment. On the other hand, there are other studies that claim that CO occurrence in DKA is the result of aggressive treatment for DKA control.

3. EO demographic aspects in DKA

The incidence of CO in DKA is difficult to determine (Edge, 2000). Following the literature review, it was found that the incidence of EO in pediatric patients with DKA is 0.5-0.9% (Hanas et al., 2007; Lawrence et al., 2005). In the case of adults, it seems that the incidence of EO in those with DKA is lower - 0.03% (McIntyre et al., 2000; Hiller & Wolf, 2005; Edge et al., 2001). Even if CO is less commonly found in diabetic adults than pediatric patients, the mortality rate is higher - 35% (Siwakoti et al., 2017), compared with the incidence of the mortality rate identified in children by Edge et al. (24%) (Edge et al., 2001), Glaser et al. (21%) (Glaser et al., 2001) and Lawrence et al. (23%) (Lawrence et al., 2005). People with various associated comorbidities are at higher risk of CO installation, probably due to a deficient homeostatic mechanism that is unable to adjust the imbalances that occur during the installation and treatment of DKA.

4. Risk factors

The following eight risk factors were mainly incriminated in the development of cerebral edema: patients treated with sodium bicarbonate, high serum levels of Blood Urea Nitrogen (BUN), low PaCO₂, low serum bicarbonate, young age, newly diagnosed diabetes, ketoacidosis onset, fast-paced hydration therapy.

Another important element is the slow increase in serum sodium during therapy correlated with rapid decrease in blood glucose levels by

insulin administration. Since both glucose and sodium are osmotically active, the previously described phenomenon will lead to decreased plasma osmolality with intraneuronal plasma influx, followed by cerebral edema.

Studies conducted are mostly retrospective studies without control groups (Cameron et al., 2005). Studies conducted by Glaser and colab. (Glaser et al., 2001; Glaser et al., 2004) Lawrence and colab. (Lawrence et al., 2005) and Edge and colab. (Edge et al., 2001) are conducted with control groups. Bellos showed that hyponatremia would be an unfavorable prognostic factor (Glaser et al., 2004).

Administration of hyperosmolar fluids and fluids. Several authors (Sandu, 2020; Sandu et al, 2019; Sandu et al., 2017) 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 (Rose et al., 2000). The theory is explained by the neural protection mechanism that develops as a result of consecutive hyperosmolality of hyperglycemia. In order to maintain its normal cell volume in the context of hyperosmolality, 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 osmolality, 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 (McManus et al., 1955). These conditions promote the circulation of water from the extra environment, into the intracellular environment, with consecutive cell edema. Therefore, the risks are also associated with insulin therapy with hypoglycemic effect, which will stimulate the exchanger of Na/H^+ resulting in Na influx and water and proton efflux. The sodium-hydrogen exchange mechanism thus increases the intracellular concentration of sodium and liquids (especially hypotonic) administered to correction of dehydration. Both interventions cause a rapid decrease in serum osmolality, thus favouring the circulation of water in brain cells (Brown, 2004).

Administration of sodium bicarbonate: The risk is likely due to cellular brain oxygen depletion, secondary to a change in the oxygen dissociation curve, a phenomenon that occurs consecutively alkalization of the blood, resulting in consecutive hypoxia and hypoxemia. This phenomenon has as its seemingly paradoxical consequence, the decrease in pH at the neural level and in cerebrospinal fluid (Inward et al., 2002). Several authors argue that sodium bicarbonate therapy is dangerous and should not be used, except in cases of severe hyperkalaemia associated with myocardial dysfunctions occurring in the context of acidosis.

Intubation and hyperventilation. Marcin and colab reported that intubation and hyperventilation are independent risk factors for the development of cerebral edema (Marcin et al., 2002). This is explained by the decrease of PaCO₂, which will cause vasoconstriction and ischemic lesions of the blood-brain barrier, resulting in vasogenic oedema. In this respect, following this observation Tasker et al. claimed that patients intubated and ventilated for EO symptoms should be ventilated at levels of PaCO₂ lower than the normal range, since ventilation at normal levels of PaCO₂ represents a sudden increase in PaCO₂ in these patients, in which Pa CO₂ is lower due to hyperventilation that occurs as a compensating mechanism of the acidosis. Marcin, Ackerman and colab. seem to agree to this, suggesting that patients intubated and ventilated for the EO should be ventilated up to the levels of PaCO₂ which represent their basic condition at the onset of symptoms and avoid PaCO₂ too high or too low. Ventilation with subsequent changes of PaCO₂ can cause either additional cerebral vasoconstriction and may worsen ischemia, or cause cerebral vasodilation and increased intracranial pressure (Marcin et al., 2002).

Hoffman, using transcranial Doppler ultrasound in five patients, found an increase in pulsability index, which suggests an increase in intracranial pressure due to the existence of cerebral vasoplegia based on low brain reactivity before treatment and 6 hours after initiation of treatment. There was a return of vascular tonus at 24 hours with full normalization at 48 hours. Their findings favour a vasogenic mechanism for CEDKA formation. Cerebral vascular altered can be mediated by an increase in prostaglandin I₂ produced by adipose tissue, as found in a DKA rat model. Several authors indicate that the risk of EO appears to be related to the severity of acidosis and that it is related to metabolic disturbances that cause cerebral oedema. Several authors indicate that the risk of developing CEDKA cannot be caused at all by treatment, but rather to the severity of acidosis, while suggesting that EO development is unpredictable (Lam et al., 2005).

5. CO before treatment of DKA

According to some authors (Mahoney et al., 1999), the appearance of CO during DKA installation can be clearly explained pathophysiologically. Usually a late-onset DKA occurs in people newly diagnosed with diabetes, which means an important hyperosmolality and implicitly a significant CO, according to some authors (Arieff & Kleeman, 1973). The process is based on the presence of excessive hyperosmolality with the potential of

developing a cerebral edema of cytotoxic origin, by affecting the structure of the cerebral parenchyma. When hyperosmolality develops, following hyperglycemia, nerve cells accumulate osmoprotective molecules, largely represented by taurine and myo-inositol (Arieff & Kleeman, 1973). Also, due to the existence of the blood-brain barrier, the diffusion of water occurs practically instantaneously, but with the delay of the diffusion rate of electrolytes up to 6 hours (Arieff & Kleeman, 1973). When the plasma level of sodium chloride is lower than the level of sodium chloride in the cerebrospinal fluid, water is effectively drawn into the cerebral parenchyma, precisely by the presence of those osmoprotective molecules. Finally, the swelling of these brain cells practically occurs, the consequence being the increase of the volume of the brain (Mahoney et al., 1999; Arieff & Kleeman, 1973).

6. CE during treatment of DKA

Other researchers have suggested that DKA treatment may lead to EO implantation (Harris et al., 1990; Vlcek, 1986; Mahoney et al., 1999; Duck et al., 1976; Duck & Wyatt, 1988; Harris & Fiordalisi, 1994; Van Der Meulen et al., 1987). The asserted theory would be due 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 EC. 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 EC implantation (Klekamp & Churchwell, 1996).

Even if this conception starts from some processes that can be explained physiopathologically, until nowadays the specialized literature has not been able to reach a clear consensus. Studies that incriminate the EC installation by the differences of osmolality installed quickly following a hyperhydration failed to establish a concrete causal chain. Moreover, there are numerous studies that mention the lack of continuity between hydration therapy in DKA and the occurrence of CO (Rosenbloom & Hanas, 1996).

7. Treatment

Given the inconclusive nature of the current literature, no treatment strategy can be definitively recommended (Tomaziu-Todosia, 2019). Some studies have suggested that intense hydration leading to rapid changes in osmolality may be associated with CO, but do not have sufficient methodology to suggest a causal relationship. Other important studies show no relationship between hydration treatment and CO. The extent of the proposed rehydration protocols should be left to the attending physician, but the rate of dehydration, acidosis level, serum osmolality and serum glucose concentration should be taken into account. However, currently the treatment of cerebral edema should be aimed at hydration, insulin therapy, electrolyte therapy, administration of sodium bicarbonate.

Certainly the best way to prevent CEDKA is to prevent DKA. With regard to insulin therapy there has been a change over time from recommendations for bolus doses to continuous infusion insulin, more prudent administration of liquids and avoiding as much as possible sodium bicarbonate.

Fluid management. It seems prudent to avoid excessive amounts of liquid, liquid administered too quickly and the use of hypotonic solutions. Most authors do not recommend that a liquid bolus be given unless there are extreme tachycardia or signs of hypovolemic shock (hypotension, cold extremities and /or anuria). If a bolus is administered to correct haemodynamic instability, it is not recommended to continue bolus once haemodynamic stability is achieved. It is recommended to use isotonic solution (0.9%) sodium chloride for bolus and to correct deficits. Maintenance fluids may be administered as 0.45% sodium chloride solutions.

Deficits should be estimated at 5% to 7% weight, unless shock is present, if they involve losses of 10% to 15% body weight. Fluid deficit replacement is at a speed of 1/48 per hour within 48 hours.

Insulin administration. Bolus insulin is no longer used in paediatric patients. Insulin administration is done at a rate of 0.1 unit / kg / hour (McManus et al., 1995). This is a recommendation of the European and American Endocrinology Societies based on controlled clinical trials. Many authors and clinicians recommend 0.05 units / hour. If blood sugar drops by a speed of 50 mg / dL / hour or if the blood sugar does not begin to correct in 2-4 hours, increase the insulin dose to 0.15 units / kg / hour. If blood sugar drops to 350 mg / dL or 100 mg / dL / hour, add glucose in the ratio of 4-5 g / insulin unit. Many clinicians do not allow blood glucose to decrease by 50 –100 mg / hour. Due to the large frequent decrease in blood

glucose observed with initial fluid therapy, some clinicians do not start insulin therapy until after the initial liquid bolus (Marcin et al., 2002).

Administration of sodium bicarbonate. It is difficult to justify a total ban on the use of sodium bicarbonate. It can be administered at a dose of 0.5-1.0 mEq / kg above 30 - 60 minutes in patients at high risk of decompensation due to deep acidosis.

Various definitions of severe acidosis, including pH 7.1, 7.0, and 6.9, are used. Although it is not completely certain that sodium bicarbonate is dangerous, there is no evidence that it would be beneficial in these patients.

Correction of dyselectrolytemia. It is not known whether the natremia decreases as a consequence of the failure of sodium to increase during treatment or decrease is the consequence of sodium cellular influx, which causes the EO. Another theory of hyponatremia claims that it is caused by already existing brain damage (Inward et al., 2002). In both cases, isotonic solution (0.9%) is recommended sodium chloride in bolus. Patients usually also associate hypokalaemia with hypophosphataemia. Potassium depletion is between 3–6 mmol / kg, and insulin administration will increase this by attracting intracellular potassium. Proper potassium replacement can help prevent arrhythmias. Phosphate deficiencies are generally between 0.5-2.5 mmol/kg and should also be corrected (Cameron et al., 2005).

Specific measures also includes osmotherapy, diuretics, corticotherapy.

Osmotherapy. The most popular drug agent used for this purpose is mannitol. Mannitol is used intravenously at doses of 1 g/kg. During the use of mannitol, the osmolarity of the plasma will be monitored, which will be maintained within the limits of 300-310 mOsm/l.

Diuretics. Of which the most used are loop diuretics, and can be used as monotherapy or as an adjunct treatment in osmotherapy. The recommended dose of furosemide is 0.7 mg/kg (Hiller & Wolf, 2005).

Corticotherapy. Corticosteroids are mainly effective in combating vasogen oedema, given their property to reduce vascular permeability. Edema may respond to high-dose injections of dexamethasone.

8. Thanatogenesis

The severity of cerebral edema varies and depends on the degree of severity. If the cerebral oedema is sufficiently advanced to cause intracranial hypertension and especially if left untreated, the patient will die. This fact is due to the compression mechanism involved on the brain which, under the conditions of a skull bone container that cannot be enlarged, the whole force

will be supported by the brain itself. Thus, cones of pressure are produced, respectively herniation that trigger the cardio-respiratory insufficiency of central origin, with irreversible evolution towards death.

9. Conclusions

The mechanisms that determine the occurrence of CO in DKA are most likely numerous and a tangled interaction of many of the pathways discussed. It is obvious that the mechanism involved in maintaining brain cell integrity during osmolality stress is extremely important. Unfortunately, the changes following the hydro-electrolyte imbalances in the installation and treatment of DKA, remain an area that is not fully elucidated. Even if this topic has been of interest to the research field, the cases on which studies have been conducted are insufficient and incomplete. This may be due, on the one hand, to the insufficient number of cases, due to the low incidence of CO in DKA, and on the other hand the lack of case-control groups. Attention should also be given to the time and place of initiation of treatment, an eventual association with certain risk factors, as well as the degree of severity of both DKA and CO. Therefore, there are many aspects to consider in order to understand clearly the mechanisms that determine the installation of CO in DKA. The path of elucidation is a long one, being beneficial any analysis of these theories, that can raise new questions that later can direct to possible new orientations/ explanations.

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