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Review

Brain edema in diseases of different etiology

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ABSTRACT

Cerebral edema is a potentially life-threatening complication shared by diseases of different etiology, such as diabetic ketoacidosis, acute liver failure, high altitude exposure, dialysis disequilibrium syndrome, and salicylate intoxication. Pulmonary edema is also habitually present in these disorders, indicating that the microcirculatory disturbance causing edema is not confined to the brain. Both cerebral and pulmonary subclinical edema may be detected before it becomes clinically evident. Available evidence suggests that tissue hypoxia or intracellular acidosis is a commonality occurring in all of these disorders. Tissue ischemia induces physiological compensatory mechanisms to ensure cell oxygenation and carbon dioxide removal from tissues, including hyperventilation, elevation of red blood cell 2,3-bisphosphoglycerate content, and capillary vasodilatation. Clinical, laboratory, and necropsy findings in these diseases confirm the occurrence of low plasma carbon dioxide partial pressure, increased erythrocyte 2,3-bisphosphoglycerate concentration, and capillary vasodilatation with increased vascular permeability in all of them. Baseline tissue hypoxia or intracellular acidosis induced by the disease may further deteriorate when tissue oxygen requirement is no longer matched to oxygen delivery resulting in massive capillary vasodilatation with increased vascular permeability and plasma fluid leakage into the interstitial compartment leading to edema affecting the brain, lung, and other organs. Causative factors involved in the progression from physiological adaptation to devastating clinical edema are not well known and may include uncontrolled disease, malfunctioning adaptive responses, or unknown factors. The role of carbon monoxide and local nitric oxide production influencing tissue oxygenation is unclear

1. Introduction

Cerebral edema may develop in a variety of unrelated diseases, being a complication shared by diabetic ketoacidosis, acute liver failure, high altitude exposure, the time period after the first dialysis procedure, and salicylate poisoning (Fig. 1). Development of brain swelling during the clinical course of these conditions is potentially life-threatening as it raises intracranial pressure and may progress to brain herniation and death. Pulmonary edema consistently accompanies brain edema in all of these disorders. Clinical, laboratory, and post-mortem findings reveal that intracellular acidosis and/or tissue cells hypoxia are features shared by all of these diseases. Tissue ischemia occurring in these conditions induces compensatory mechanisms intended to enhance oxygen delivery to cells and carbon dioxide removal from tissue cells, such as hyperventilation, a rise in the erythrocyte 2,3-bisphosphoglycerate concentration (to reduce the affinity of hemoglobin for oxygen), and capillary vasodilatation. These adaptive mechanisms develop to maintain tissue oxygenation and intracellular acid–base balance in tissue cells under metabolic stress, but severe uncontrolled diseases that overcome the physiological responses, defective compensatory mechanisms, and therapeutic or unknown factors may result in worsening tissue hypoxia that may induce unwarranted capillary vasodilatation with increased vascular permeability and plasma fluid extravasation leading to cerebral and pulmonary interstitial edema. A striking whole-body escape of plasma into the interstitium typically occurs during episodes of systemic capillary leakage syndrome, a rare disease of unknown cause in which cerebral edema and pulmonary edema have also been reported.

Abbreviations: ALF, acute liver failure; BBB, blood–brain barrier; CSF, cerebrospinal fluid; CT, computed tomography; DKA, diabetic ketoacidosis; FHF, fulminant hepatic failure; HACE, high altitude cerebral edema; HAPE, high altitude pulmonary edema; MRI, magnetic resonance imaging; pCO_2, partial pressure of carbon dioxide; VEGF, vascular endothelial growth factor.

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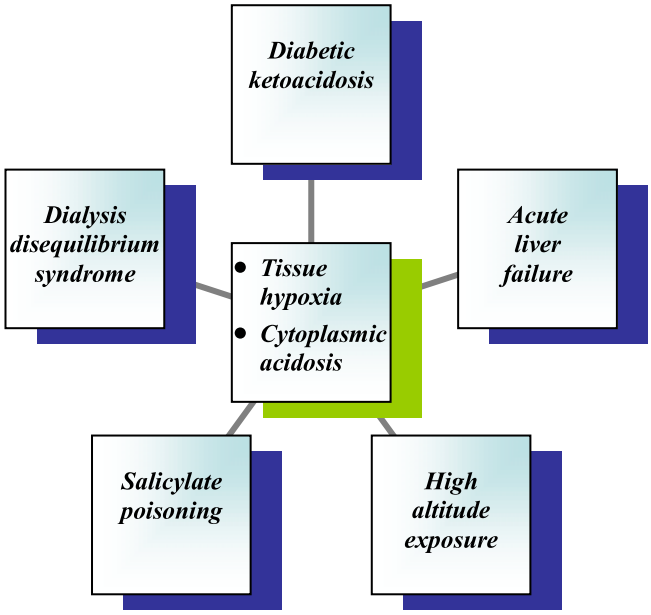

Fig. 1. Diseases leading to cerebral edema share tissue hypoxia or intracellular acidosis.

2. Cerebral edema and diabetic ketoacidosis

Cerebral edema is a rare but life-threatening complication of diabetic ketoacidosis (DKA) that occurs predominantly in children, although it was first described and has been reported in adults (Dillon et al., 1936; Haringhuizen et al., 2010; Hayes and Woods, 1968). The incidence of DKA-related cerebral edema in prospective population-based studies from the USA, UK, Canada, and Sweden is similar, ranging from 0.51% to 0.68% (Edge et al., 2006a; Hanas et al., 2007; Harris et al., 1990; Lawrence et al., 2005). Approximately 21–24% of the affected patients die and 15–35% survive with permanent neurologic dysfunction (Edge et al., 2006a; Glaser et al., 2001; Lawrence et al., 2005).

The clinical picture is characterized by a sudden neurological deterioration with coma, dilatation of the pupils, sluggish pupillary reaction, and papilledema that typically occurs within 24 h after the initiation of therapy, although 5–19% of the patients display clinically apparent cerebral swelling at initial presentation. Subclinical brain edema detected by neuroradiologic imaging is a frequent occurrence both before the therapy is initiated and during the treatment of DKA episodes (Hoffman et al., 1988). Contrast-enhanced perfusion and diffusion magnetic resonance imaging (MRI) scans have revealed an increase in blood–brain barrier (BBB) permeability during treatment (Vavilala et al., 2010).

In 1968, pulmonary congestion was reported among the post-mortem findings in an adult case with DKA who died from cerebral edema (Hayes and Woods, 1968). Since then, pulmonary edema has been regularly documented in DKA. Typically, patients display respiratory insufficiency with hypoxemia and rales are noted on auscultation. Chest X-rays films show interstitial edema and pulmonary artery wedge pressures are consistently normal (Brun-Buisson et al., 1985; Haringhuizen et al., 2010; Hoffman et al., 1998; Rosenbloom et al., 1980; Rosenbloom and Schatz, 1990). High resolution computed tomography (CT) findings suggest that subclinical interstitial pulmonary edema is frequent prior to therapy in patients with DKA (Hoffman et al., 1998).

In 1936, structural cerebral damage was first reported associated with fatal DKA in adults. The brain showed gross and microscopical changes reminding those seen in cerebral hypoxia, including dilatation of capillary beds and cerebral edema (Dillon et al., 1936). Subsequent post-mortem examinations have shown similar changes. Grossly, the whole brain is markedly congested and edematous. Microscopical studies disclose degeneration, and necrosis of the nerve cells with astrocyte swelling, and extensive perivascular, pericellular and interstitial edema of the brain (Haringhuizen et al., 2010; Hayes and Woods, 1968; Hoffman et al., 2009; Rosenbloom et al., 1980). Activated microglial cells around the capillaries and BBB disruption with albumin extravasation have recently been observed (Hoffman et al., 2009). Pulmonary edema has been also noted in post-mortem examinations and attributed to altered alveolocapillary permeability. Necropsy findings in other tissues also suggest increased vascular permeability (Brun-Buisson et al., 1985; Haringhuizen et al., 2010; Hayes and Woods, 1968).

A number of retrospective studies and some prospective uncontrolled data have evaluated possible predictive factors for the appearance of DKA-related cerebral edema. Rate of fluid infusion, plasma osmolality, negative sodium trend (failure of the plasma sodium concentration to rise as glucose declines during DKA therapy), lower diastolic blood pressure, more rapid correction of plasma pH, intubation with hyperventilation to an arterial partial pressure of carbon dioxide (pCO_2) less than 22 mm Hg, and treatment with bicarbonate have been reported as potential risk factors for cerebral edema in the setting of DKA (Bello and Sotos, 1990; Duck and Wyatt, 1998; Durward et al., 2011; Edge et al., 2006a; Glaser et al., 2001, 2008; Hale et al., 1997; Harris et al., 1990; Harris and Fiordalisi, 1994; Hom and Sinert, 2008; Lawrence et al., 2005; Mahoney et al., 1999; Marcin et al., 2002; Mel and Werther, 1995; Rosenbloom and Schatz, 1990). Multivariate analyses in retrospective studies find an association between cerebral edema and more severe acidosis and hypocapnia at DKA presentation (Edge et al., 2006a,b; Glaser et al., 2001; Mahoney et al., 1999). A nested case-control study shows that cerebral edema is associated with lower initial plasma pH and bicarbonate level, although the baseline arterial pCO_2 was not significantly lower in cases than control subjects (Lawrence et al., 2005). In a small prospective study, brain edema on admission detected by CT scan correlated inversely with serum bicarbonate concentration at presentation and at 6 h (Durr et al., 1992). Multiple logistic regression analysis reveals that lower initial arterial pCO_2 level is significantly associated with cerebral edema quantified by MRI while no other variables analyzed were associated with ventricular narrowing in the multivariate analysis (Glaser et al., 2006). Further, the extent of edema formation during DKA quantified by MRI is correlated with the degree of hyperventilation at presentation (Glaser et al., 2008).

The pathogenic mechanisms underlying the development of DKA-related brain edema are unclear. Cerebral blood flow has been found normal to increased 6 h after the start of therapy despite hypocapnia. Lowered cerebral oxygen uptake has been observed in fatal adult cases of DKA (Kety and Polis, 1948a). The normal response of the cerebral resistance vessels to changes in arterial blood pressure to maintain stable cerebral blood flow (cerebral autoregulation) is diminished at 6 h and normalizes by 36 h after DKA therapy (Roberts et al., 2006). Prior to treatment, patients with DKA suffer an intense acid–base disturbance consisting of severe metabolic acidosis primarily due to production of ketone bodies, although lactate and other anions also may contribute. Plasma chloride is consequently reduced. Metabolic acidosis induces marked hyperventilation which in turn reduces blood carbon dioxide content (Funk et al., 2003; Hale et al., 1984). Post-treatment, most patients attain blood pH values of 7.35 or greater, but the pCO_2 remains low, implying that hyperventilation persists despite correction of plasma metabolic acidosis, generating respiratory alkalosis during the recovery phase. Accordingly, plasma chloride concentration is elevated after DKA therapy (Winters et al., 1958). Patients with DKA show normal cerebrospinal fluid