Brain edema in diseases of different etiology

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Available online 9 May 2012
Accepted 1 May 2012
Received in revised form 23 April 2012
Received 6 March 2012

Article history:
Article info
Keywords:
Diabetic ketoacidosis
Acute liver failure
High altitude exposure
Dialysis disequilibrium syndrome
Salicylate poisoning
2,3-Bisphosphoglycerate

Cerebral edema and pulmonary edema have also been reported. 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.

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.
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 microscopic 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 alveolo-capillary 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 (pCO₂) 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 Fjordalisi, 1994; Hom and Sinert, 2008; Lawrence et al., 2005; Mahoney et al., 1999; Marcin et al., 2002; Mel and Werthber, 1995; Rosenbloom and Schatz, 1990). Multivariate analyses in retrospective studies find an association between cerebral edema and more severe acidosis and hypopcarpia 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 pCO₂ 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 pCO₂ 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 hypopcarpia. 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 pCO₂ 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
(CSF) pH values before the initiation of treatment, but a striking fall in CSF pH is observed during the first hours into therapy concurrently with the correction of blood acidosis, while bicarbonate levels in CSF remain unchanged despite intravenous infusion of bicarbonate. The sharp fall in CSF pH appears to be due mainly to a significant rise in CSF pCO₂ (Assal et al., 1974). It has been observed that the red blood cell concentration of 2,3-bisphosphoglycerate is markedly reduced in DKA patients prior to therapy (Ditzel and Standl, 1975), probably due to insulin deficiency preventing glucose from entering the red cells and perhaps to the need to spare glucose to maintain energy production, as 2,3-bisphosphoglycerate formation does not result in ATP formation. Reduced 2,3-bisphosphoglycerate level inside the red cell contributes to intensify tissue ischemia by restraining oxygen unloading from erythrocytes to tissue cells along capillaries. In contrast, erythrocytes of controlled diabetic subjects contain significantly more 2,3-bisphosphoglycerate than normal individuals, suggesting a baseline degree of tissue acidosis with a compensatory rise in red cell 2,3-bisphosphoglycerate level (Ditzel et al., 1973).

3. Cerebral edema and acute liver failure (fulminant hepatic failure)

Acute liver failure (ALF) or fulminant hepatic failure (FHF) may be defined as the abrupt onset of severe liver injury in a patient without pre-existing liver disease that may be complicated with systemic infection, hyperdynamic circulation, bleeding diathesis, cerebral edema leading to intracranial hypertension, and multi-organ failure, including adult respiratory distress syndrome and kidney failure. FHF is a rare but life-threatening condition, with an estimated incidence of 2000 cases per year in the US. Mortality rate is approximately 33%, while 25% of the patients undergo orthotopic liver transplantation, and the remainder 42% recover spontaneously (Lee, 2003).

Development of cerebral edema is a well-documented complication of FHF and a major cause of mortality. Similarly to DKA, cerebral swelling in ALF is more common in young patients and the clinical picture includes coma, dilated pupils with sluggishly reaction to light, papilledema, and potentially brain herniation. The encephalopathy caused by ALF usually reverses completely after spontaneous recovery or liver transplantation, but irreversible brain damage may remain in some patients (Aggarwal et al., 1994; Ware et al., 1971; Wendon et al., 1994). Non-cardiogenic pulmonary edema has been noticed accompanying brain edema in ALF (Lee, 2003; Trewby and Williams, 1977).

Brain swelling is present in 38–50% of the patients with ALF whose brains are examined at autopsy (Ware et al., 1971). Microscopically, cerebral edema associated with ALF is localized to the perivascular space and large swollen astrocytes are observed (Laursen, 1982; Ware et al., 1971). Scanning electron microscopy images show marked swelling of endothelial cells, basement membranes, pericytes, and astroglial foot processes, with increased number of vesicles and vacuoles indicative of passage of fluid through capillaries (Kato et al., 1992).

Predictive factors for the occurrence of brain swelling in FHF patients have been analyzed by a number of studies. In a large cohort of patients with ALF, multivariate analysis reveals that the risk for intracranial hypertension is independently associated with requirement for vasopressors and dialysis and with age less than 45 years. The adjusted hazard ratios for elevated blood ammonia concentration and risk for intracranial hypertension and severe encephalopathy are 1.01 and 1.008, respectively, in this cohort, suggesting that other factors besides hyperammonemia are important in producing brain edema during FHF (Bernal et al., 2007). Further, there is remarkable inter-individual variation in the blood ammonia concentration among patients with ALF and considerable overlap of blood ammonia values is observed among patients with and without cerebral edema (Bhatia et al., 2006; Clemmesen et al., 1999; Davern, 2007; Kundra et al., 2005; Schwartz et al., 1953; Tofteng et al., 2006; Tyor and Sieker, 1959; Vanamee et al., 1956).

The pathogenesis of FHF-associated cerebral edema is mostly unknown. Measurements of cerebral blood flow in FLF have shown wide heterogeneity between patients and also intra-individually (Aggarwal et al., 1994; Wendon et al., 1994). Reduction of cerebral oxygen consumption in comatose patients with ALF has been consistently found, although the prognostic significance of this metabolic derangement is uncertain, as patients with severe low brain oxygen consumption during hepatic coma have recovered without neurological sequelae (Aggarwal et al., 1994; Wendon et al., 1994; Strauss et al., 2003). Cerebral autoregulation is reduced in patients with FHF, being restored after spontaneous hepatic recovery or liver transplantation (Strauss et al., 1997). Similarly, the normal response of cerebral vasculature to changes in arterial pCO₂, particularly hypercapnia, is attenuated in patients with FHF (Durham et al., 1995). Patients with ALF experience a widespread hemodynamic disturbance with reduced peripheral and splanchic vascular resistance leading to arterial hypotension with normal central venous pressure and pulmonary artery wedge pressure. The cardiac output and heart rate are consequently increased creating a “hyperdynamic circulation” (Bihari et al., 1985a, 1985b; Trewby and Williams, 1977). It has been observed that tissue hypoxia develops in patients with ALF, being more severe in non-survivors (Bihari et al., 1985b). Plasma acid–base balance is profoundly altered in patients with ALF. Hyperventilation is observed in most ALF patients and consequently arterial pCO₂ is low, although plasma pH may be normal (Aggarwal et al., 1994; Durham et al., 1995; Kosaka et al., 1979; Record et al., 1975; Strauss et al., 2003). Elevations of blood lactate, pyruvate, and other organic anions such as α-ketoglutarate, citrate, succinate, fumarate, acetoacetate, and β-hydroxybutyrate have been regularly observed in FHF patients (Amatuzio and Nesbitt, 1950; Bihari et al., 1985a; Record et al., 1975; Strauss et al., 2003). Hypoaluminiemia bearing an alkalizing effect is a frequent occurrence in ALF (Funk et al., 2006). The erythrocyte concentration of 2,3-bisphosphoglycerate is significantly more elevated in patients with ALF than in healthy controls, implying defective tissue oxygenation that needs to be compensated by reducing hemoglobin affinity for oxygen to facilitate oxygen release to tissue cells (Bihari et al., 1985b; Hurt and Chanutin, 1965).

4. Cerebral edema and hypobaric hypoxia of high altitude

High altitude disease may occur in unacclimatized individuals who are rapidly exposed to height greater than 2500 m. It may be prevented by gradual ascent with adaptation periods to each new elevation. The onset of symptoms typically occurs within 2–4 days after arrival although it may occur while descending after ascent. Altitude illness may be manifested as acute mountain sickness, high altitude pulmonary edema (HAPE), high altitude cerebral edema (HACE), or a combination of them. The prevalence of acute mountain sickness increases with altitude, being 9% at 2850 m, 13% at 3050 m, 34% at 3650 m, and 53% at 4559 m (Maggiorgini et al., 1990). Most serious forms of altitude sickness such as HAPE and HACE occur in approximately 0.5–1.0% of climbers to elevations above 4500 m. Altitude sickness is the cause of 13–25% of the deaths among trekkers (Hultgren, 1979).

The clinical picture of acute mountain sickness consists of a general feeling of malaise, headache, drowsiness, arterial hypotension, peripheral edema, insomnia, and dyspnea on exertion. More severe and potentially life-threatening disease is characterized by
the appearance of HAPE, HACE, or both, which are frequently heralded by oliguria. HAPE symptomatology includes cough, dyspnea, hemoptysis, and crackles on lung auscultation. Chest X-rays reveal patchy infiltrates throughout the pulmonary fields (Hultgren et al., 1964; Hultgren, 1979; Kobayashi et al., 1987). Cardiac catheterization studies show pulmonary hypertension due to hypoxic pulmonary arteriolar constriction and normal or low pulmonary artery wedge pressure (Hultgren et al., 1964). Alveolar edema fluid obtained by bronchoalveolar lavage in HAPE patients is rich in high molecular weight proteins and cells, suggesting an increase in pulmonary vascular permeability. Neurological alterations and cerebral edema detected in computerized tomogram are very common in patients with HAPE, underlying the continuum between high altitude sicknesses (Kobayashi et al., 1987). HACE clinical features include ataxia, mental confusion, seizures, and lethargy progressing to stupor or coma. Papilledema and retinal hemorrhages are usually present in HACE episodes and lumbar puncture reveals increased CSF pressure. Late neurologic complications are rare and mental processes appear to recover completely (Hultgren, 1979). Diffusion-weighted MRI studies have identified mild astrocytic swelling associated to high altitude (Bailey et al., 2009).

The main autopsy findings in high altitude diseases are prominent edema of the lungs and brain. On histological examination, striking dilatation of precapillary arterioles and capillaries with perivascular leakage of blood is noted in all the organs (Dickinson et al., 1983; Hultgren, 1979; Singh et al., 1965).

Besides too rapid an ascent, the only known predisposing factor to the disease is prior occurrence of altitude sickness. Some genetic polymorphisms in the genes that encode aldosterone synthase and angiotensin-converting enzyme have been documented to occur more frequently in persons adapted to altitude, but their clinical significance regarding predisposition to mountain sickness is unclear (Wilson et al., 2009). It has been reported a Han Chinese family with multiple members affected with HAPE in which only the hypoxia inducible factor HIF2A haplotype was shared by individuals who exhibit the HAPE phenotype (Lorenzo et al., 2009).

Defective physiological responses to hypobaric hypoxia bring about altitude sickness. The concentration of inspired oxygen is 21% in dry atmospheric gas at any altitude. Barometric pressure and therefore the concentration of oxygen available to reach the alveoli during ventilation are reduced at high altitude. Hyperventilation with an increase in depth and rate of breathing is an immediate essential adaptation to acute high altitude exposure, leading to respiratory alkalosis (Leissner and Mahmood, 2009; West, 1971). Cardiac catheterization studies show pulmonary hypertension due to hypoxic pulmonary arteriolar constriction and normal or low pulmonary artery wedge pressure (Hultgren et al., 1964). Diffusion-weighted MRI studies have identified mild astrocytic swelling associated to high altitude (Bailey et al., 2009).

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5. Cerebral edema and dialysis disequilibrium syndrome

An acute neurologic deterioration with cerebral edema and occasionally pulmonary edema following hemodialysis has been consistently documented since 1961 and it is referred to as dialysis disequilibrium syndrome. The neurological disturbance generally occurs within 24 h after the first dialysis procedure, when blood biochemical parameters have improved. Patients may experience headache, drowsiness, blurred vision, nausea and vomiting. More severe cases are characterized by consciousness deterioration, seizures, coma, and sometimes brain herniation and death. Necropsy findings show severe brain swelling (Rosen et al., 1964). Magnetic resonance imaging in patients on regular dialysis demonstrate that a mild increase in cerebral volume occurs following dialysis sessions (Walters et al., 2001). Erythrocyte concentrations of 2,3-bisphosphoglycerate have been reported more elevated in uremic patients than in controls, suggesting some degree of baseline tissue ischemia or acidosis (Hurd and Chanutin, 1964). The pathogenesis of the syndrome is poorly understood, but rapid correction of plasma metabolic acidosis or other metabolic alterations present in the uremic state may contribute. Prior to the dialysis procedure uremic patients typically exhibit plasma metabolic acidosis. Dialysis improves this acid–base disturbance by elevating plasma bicarbonate level, but most patients after dialysis display sustained low carbon dioxide content in blood despite normalization of the acidosis, denoting the occurrence of persistent hyperventilation that results in respiratory alkalosis in the post-dialysis period, similarly to the recovery phase of DKA (Weller et al., 1953; Winters et al., 1958).

6. Cerebral edema and salicylate intoxication

Salicylate intoxication is a severe condition with a mortality rate of 15% that has been regularly associated with cerebral and pulmonary edema (Thisted et al., 1987). Salicylate poisoning is typically associated with a mixed acid–base pattern that consists of a primary metabolic acidosis and a primary respiratory alkalosis. Blood carbon dioxide content is uniformly reduced, although plasma pH may be normal, acid or alkaline (Thisted et al., 1987; Winters et al., 1959). Similarly to other conditions featuring metabolic acidosis, such as uremia and DKA, patients with salicylate poisoning continue to hyperventilate despite the correction of serum bicarbonate so that the blood pCO2 remains at a low level during the recovery period of the disease (Winters et al., 1959).

7. Cerebral edema and systemic capillary leakage syndrome

Systemic capillary leakage syndrome is a rare life-threatening disorder of undetermined etiology and pathophysiology characterized by recurrent episodes of increased capillary permeability to plasma, resulting in massive extravasation of large molecules and...
serum into the interstitial space with severe reduction of the intravascular volume reflected by vast hemocoagulation and hypalbuminemia. Massive anasarca with swelling of the face, arms, and legs is produced by rapid increase of extravascular fluid. The end of the episode is characterized by rapid shift of fluid to the intravascular space that induces a period of massive diuresis and diminution of peripheral edema. A family with several affected members has been reported (Sion-Sard et al., 2010). Clinically, patients describe a feeling of generalized malaise and progressive reduction of diuresis in the hours preceding an attack, followed by diffuse subcutaneous edema with weight gain after 2–3 h. The attack resolves in the next 36–48 h and fluid and protein return to the intravascular space inducing polyuria (Agostoni et al., 1992). The similarity between this sequence of events and the pattern of body fluids modification during high altitude exposure, with fluid retention and generalized edema preceding polyuria and weight loss, is remarkable. In high altitude adaptation, fluid retention is presumably driven by hypoxia-related systemic capillary dilatation, but the cause remains elusive in systemic capillary leakage syndrome. Brain edema and pulmonary edema have been documented associated with this syndrome and their occurrence has been confirmed in post-mortem examinations (Agostoni et al., 1992; Bertorini et al., 1997).

8. Tissue ischemia and brain edema

Cerebral edema is a devastating complication that may develop during the clinical course of DKA, ALF, high altitude disease, dialysis disequilibrium syndrome, and salicylate poisoning. (Table 1) Along with cerebral edema, pulmonary edema and sometimes edema in other locations is consistently observed in all of these conditions both clinically and pathologically. Available evidence indicates that tissue hypoxia or intracellular acidosis affecting the brain and other organs occurs in all of them. Hypobaric hypoxia of high altitude induces tissue hypoxia whereas accumulation of a variety of organic anions generates intracellular acidosis in DKA, FHF, uremia, and salicylate poisoning. Furthermore, reduction of cerebral oxygen consumption in patients with cerebral edema associated with DKA and ALF has been consistently observed. Accordingly, cerebral autopsy findings in these diseases are similar to those encountered in brain hypoxic damage. Tissue hypoxia and intracellular acidosis activate compensatory mechanisms intended to facilitate oxygen delivery to cells and to ensure carbon dioxide extraction (therefore promoting excess acid elimination), including hyperventilation, elevation of erythrocyte 2,3-bisphosphoglycerate concentration, and capillary vasodilation (Fig. 2).

8.1. Hyperventilation

Hyperventilation is a physiological response to tissue hypoxia or metabolic acidosis. Intracellular pH is more effective than plasma pH in eliciting adaptive responses, as it reflects cellular metabolic status and therefore intracellular acidosis is the fundamental anomaly triggering hyperventilation (Tizianello et al., 1977). In turn, hyperventilation reduces plasma pCO2. Clinical evidence confirms that hyperventilation and low plasma pCO2 is a feature shared by all of the described conditions resulting in cerebral edema. In addition, it has been noted that rapid correction of plasma metabolic acidosis with bicarbonate paradoxically worsens cytoplastic acidosis (Bellingham et al., 1971; Ritter et al., 1990; Vanamee et al., 1956) and it has been long observed that hyperventilation persists after infusion of bicarbonate in situations featuring metabolic acidosis, such as DKA, uremia, salicylate intoxication, diarrhea, and ammonium chloride administration (Weller et al., 1953; Winters et al., 1958, 1959). Persistent hyperventilation during the recovery phase of these disorders is presumably due to worsening intracellular acidosis secondary to bicarbonate administration. Similarly to the intracellular compartment, CSF undergoes

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**Table 1**

Characteristics of the diseases leading to brain edema.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diabetic ketoacidosis</th>
<th>Acute liver failure</th>
<th>High altitude</th>
<th>Dialysis disequilibrium syndrome</th>
<th>Salicylate poisoning</th>
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<tr>
<td>Brain edema</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</table>

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**Fig. 2.** Compensatory mechanisms of tissue ischemia.
profound acidification after plasma metabolic acidosis correction during DKA episodes, although the pathogenic significance of this fall in CSF pH regardless, development of brain edema is unclear.

8.2. Red blood cell 2,3-bisphosphoglycerate concentration

A rise in erythrocyte 2,3-bisphosphoglycerate concentration is rapidly produced in response to tissue ischemia in order to reduce the affinity of hemoglobin for oxygen and therefore to increase the amount of oxygen dispensed to cells. Laboratory data demonstrate an elevation of the red cell 2,3-bisphosphoglycerate concentration in controlled diabetes, ALF, high altitude exposure, and uremic patients, denoting a baseline status of tissue ischemia with compensatory rise in erythrocyte 2,3-bisphosphoglycerate to promote oxygen delivery to tissue cells and carbon dioxide removal. The role of carbon monoxide intensifying the precarious oxygenation status in tissues and its involvement on the development of cerebral edema in these disorders, particularly ALF, is not well known. Carbon monoxide has greater affinity for hemoglobin than oxygen and carboxyhemoglobin is produced upon its binding. Once carbon monoxide has bound hemoglobin, the protein undergoes a conformational change so that the affinity for oxygen of the remaining heme groups is enhanced, reducing oxygen delivery to cells. Thus, even small amounts of carbon monoxide bound to hemoglobin may impose marked resistance to oxygen release and precipitate hypoxia in tissues, as it was first demonstrated by Haldane in 1912 (Ayres et al., 1965). It has been shown that the effect of carbon monoxide increasing hemoglobin affinity for oxygen is due to a fall in red blood cell 2,3-bisphosphoglycerate concentration (Astrup et al., 1970). Heme-oxygenase reaction is the only known endogenous source of carbon monoxide in humans and this enzyme has been found highly up-regulated at transcriptional and protein levels in patients with ALF compared to healthy controls (Fujii et al., 2004). Blood carbon monoxide and carboxyhemoglobin concentrations have been reported significantly higher in cirrhotic patients than controls (Tarquini et al., 2009; Tran et al., 2007).

8.3. Capillary vasodilatation

Capillary vasodilatation is a physiologic mechanism that takes place in response to cellular acidosis or hypoxia aimed to improve carbon dioxide extraction and oxygen delivery to tissues under metabolic distress. Emerging evidence during the last decade suggests a major role of the red blood cells mediating this response to tissue ischemia by releasing nitric oxide, a potent vasodilatator agent with a very short life. Local oxygen demand is sensed by erythrocytes through the degree of hemoglobin deoxygenation, which is coupled to nitric oxide release. As hemoglobin becomes deoxygenated, nitric oxide is delivered to tissues to produce capillary vasodilatation, physiologically matching hemoglobin deoxygenation to vasodilatation. It has been shown that hemoglobin possesses nitrite reductase activity and that human red cells express an endothelial-type nitric oxide synthase, which allows nitric oxide formation (Crawford et al., 2006; Kleinbongard et al., 2006). Widespread peripheral vasodilatation accompanies DKA, ALF, and high altitude exposure, as indicated by the occurrence of low blood pressure, normal pulmonary wedge pressure, and increased cardiac output. Clinical data also reveal increased capillary permeability with plasma leakage into the interstitial space in these conditions. The edema fluid obtained from the alveoli in HAPE victims is abundant in proteins denoting plasma leakage from capillaries. Brain MRI images of DKA patients disclose enhanced BBB permeability during the treatment of the episode. Non-cardiogenic pulmonary edema occurs in all of these disorders along with brain edema, implying that the microcirculatory dysfunction responsible for edema is not confined to the brain. Low-grade subclinical brain and pulmonary edema may be detected by radiological imaging suggesting that some baseline degree of plasma leakage into the interstitial space occurs before it becomes clinically evident. Necropsy findings confirm the occurrence of capillary vasodilatation with increased vascular permeability and plasma leakage from capillaries in all of these disorders affecting brain, lung, and other organs. Microscopic changes found in the brain are definitely similar in all of these conditions and include capillary dilatation, extensive interstitial edema and swollen endothelial cells, astrocytes, and pericytes pointing out plasma leakage that is being contained by cells surrounding brain capillaries. Pulmonary edema has been also attributed to altered alveolocapillary permeability.

Tissue ischemia-induced adaptive mechanisms intend to facilitate carbon dioxide removal and oxygen release to tissue cells under metabolic stress in order to eliminate excess acid and maintain tissue oxygenation. Progression from this physiological adaptation to life-threatening local (brain or pulmonary) or systemic edema may occur when oxygen supply no longer matches to oxygen demand, although the factors determining this progression are unclear. Tissue ischemia or cytoplastic acidosis may become more pronounced due to severe unrelenting diseases that overwhelm the physiological responses. Bicarbonate administration may also worsen intracellular acidosis. Oxygen release to tissues may decrease due to defective or exhausted tissue oxygen delivery apparatus. The role of carbon monoxide or local nitric oxide production modifying tissue oxygenation has not been explored. When cellular oxygen demand is no longer met by oxygen supply, prominent capillary vasodilatation with increased vascular permeability and plasma leakage from capillaries may occur, giving rise to clinical edema affecting the brain and other organs.

The clinical importance of hypoxia-associated cerebral edema is highlighted by its prognostic value after cardiac arrest. Subjects with severe cerebral edema detected by CT scan have very low survival rate with conventional care. Brain CT findings estimate pre-treatment likelihood of survival after cardiac arrest (Metter et al., 2011).

9. Potential chemical mediators of cerebral edema

Brain edema has been classified as vasogenic or cytotoxic. Vasogenic edema is defined as fluid originating from blood vessels and accumulating in the extracellular space around cells, while cytotoxic edema is defined as fluid accumulating within cells. In most clinical situations both forms of edema coexist during the course of the disease because once vasogenic edema develops, cytotoxic edema generally follows (Hackett, 1999).

Compared to extravascular fluid accumulation in other body locations, brain edema is peculiar in that the skull is a rigid structure that does not allow expansion of the intracranial content so that intracranial pressure is increased with relatively small accumulation of intracranial fluid (Monroe Kelly doctrine). In addition, the interface between blood in microvessels and brain parenchyma (the BBB) shows structural and functional differences in comparison with other vascular beds, modulating the passage of plasma fluid at this location. The BBB is composed of a single layer of endothelial cells surrounded by a basement membrane upon which the foot processes of astrocytes are arranged. In addition, pericytes are perivascular cells that may participate in the regulation of vessel permeability. The endothelial cells lining brain microvessels are joined via tight junctions, which consist of a number of integral membrane proteins, such as claudins, occludins, and junctional adhesion molecules. These transmembrane proteins are anchored to the cytoplasm by a protein complex called zona occludens and other accessory proteins. The molecular structure of the tight junction proteins has been evaluated by immunohistochemistry in two
cases of fatal DKA, detecting absence of some tight junction proteins (occludin, claudin-5, zona occludens-1, and junctional adhesion molecule-1) in the brain blood vessels of the patients compared with control brain tissue (Hoffman et al., 2009). It has been reported that matrix metalloproteinases, a family of extracellular matrix-degrading enzymes, may play a role in some types of cerebral edema, as tight junction proteins including occludin and claudin-5 are susceptible to be damaged by these enzymes (Rosenberg and Yang, 2007).

The molecular mechanisms and chemical mediators contributing to brain edema in humans have not been identified. Several molecules have been hypothesized to be involved in the pathogenesis of brain edema, including reactive oxygen species (that may generate oxidative stress), aquaporin 4, vascular endothelial growth factor (VEGF), molecules involved in inflammatory responses, and plasma membrane ion channels and transporters.

In physiological conditions, reducing equivalents derived from oxidation of substrates such as glucose and fatty acids are transferred to NAD$^+$ and FAD forming NADH and FADH$_2$ in the mitochondrial matrix. These reduced compounds are then oxidized by the electron transport chain, a system of electron carriers located in the inner membrane of mitochondria and grouped into four complexes (I–IV). The transfer of electrons between the complexes is coupled with pumping of protons from the matrix to the intermembrane space to create an electrochemical gradient across the inner membrane, which provides energy to drive the synthesis of ATP by the enzyme ATP synthase (complex V). Electrons ultimately reduce oxygen (O$_2$), generating water (H$_2$O) (Fig. 3). The stepwise transfer of electrons to oxygen results in the formation of superoxide anions (O$_2^-$) and hydroxyl free radicals (OH·) and a small number of these oxygen radicals are normally released in cells (Turrens, 2003) (Fig. 4). The human brain uses approximately 25% of the basal oxygen consumption in the body, being particularly susceptible to hypoxia. ATP production in the brain drops extensively following cerebral hypoxia, deteriorating brain performance including BBB permeability. (Bailey et al., 2009). In addition, the circulating concentration of free radicals rises in hypoxia, inducing an oxidative stress that might further deteriorate BBB permeability, contributing to brain edema. The high content in iron and polyunsaturated fatty acids may predispose the brain to the oxidative damage induced by free radicals (Baneke, 2010; Hoffman et al., 2011). Oxidative stress has been suggested to have a potential role in the pathogenesis of brain edema associated with DKA. In two cases of fatal DKA, strong nitrotyrosine (a marker of oxidative injury) immunoreactivity was diffusely detected in all of the examined brain regions (Hoffman et al., 2009). It has been found an increased level of 8-hydroxyguanosine (an oxidized nucleoside derived from RNA), 4-hydroxynonenal (a biologically active carbonyl derived from polyunsaturated fatty acid peroxidation), and heme oxygenase-1 (a enzyme induced as a protective antioxidant to various forms of stress) in neurons of the hypocampus of DKA brain edema compared to controls (Hoffman et al., 2011). Oxidative stress has also been implicated in the pathogenesis of hepatic encephalopathy. In post mortem cortical brain tissue samples from patients with cirrhosis, significantly elevated levels of heat shock protein-27 and 8-hydroxyguanosine (a marker of RNA oxidation) have been found in subjects with hepatic encephalopathy compared to patients with cirrhosis but without encephalopathy, suggesting that hepatic encephalopathy may be associated with oxidative stress and RNA oxidation (Gorg et al., 2010). In addition, the pathogenesis of cerebral edema in ALF has been suggested to involve a compromised oxidative metabolism with a decrease in cerebral ATP levels. Cerebral extracellular concentration of lactate and lactate/pyruvate ratio have been found elevated in patients with ALF, further suggesting cerebral hypoxia, as oxygen shortage in the mitochondria results in the reduction of pyruvate to lactate in the cytosol (Bjerring et al., 2010).

The aquaporins are a family of transmembrane water channel proteins that play a role in water movement. Among them it has been suggested that aquaporin 4 may have a role in cerebral water transport being a potential mediator in the formation and resorption of edema fluid from the brain parenchyma in ALF (Rao et al., 2007).

The VEGF is an endothelial cell mitogen that increases vascular permeability and has been reported to be involved in the pathogenesis of peritumoral brain edema (Otsuka et al., 2004). It has been suggested that the increase in the concentration of free VEGF associated with hypoxia may have the potential to increase the BBB permeability and contribute to brain edema under hypoxic conditions (Bailey et al., 2009). Although a significant rise in the plasma concentration of VEGF is seen between sea level and 5200 m, no association has been found between this change in VEGF level and acute mountain sickness symptoms (Baneke, 2010).

Inflammatory mediators have been implicated as potential causative factors of brain edema. Increased expression of chemokine (C–C motif) ligand 2 (also known as monocyte chemotactic protein-1 or small inducible cytokine A2) and nuclear factor-kappaB (a transcription factor involved in inflammatory responses) has been detected in perivascular areas diffusely distributed in the brain parenchyma (Hoffman et al., 2009).
The hypoxic suppression of the BBB ion-pumping activity may contribute to the accumulation of extracellular fluid (Bailey et al., 2009). Other chemical mediators that have been implicated as potential intermediaries in the pathogenesis of cerebral edema include angioptiogens, vasoactive inflammatory agents such as kinins (bradykinins and tachykinins), and cytokines (Nag et al., 2009).

In summary, brain and pulmonary edema may develop during the course of disorders of diverse etiology such as DKA, ALF, high land snows, dialysis disequilibrium syndrome, and salicylate poisoning, being a devastating complication with high mortality. All of these conditions feature tissue hypoxia or intracellular acidosis. Tissue ischemia induces compensatory mechanisms intended to improve tissue oxygenation and carbon dioxide removal, such as hyperventilation, erythrocyte 2,3-bisphosphoglycerate elevation, and capillary vasodilatation. When these adaptive mechanisms are unable to compensate tissue ischemia or acidosis, a mismatch between oxygen supply and oxygen demand is established and severe capillary dilatation with increased vascular permeability and massive plasma leakage leading to interstitial edema may occur. Necropsy findings in these disorders confirm the presence of cerebral hypoxic changes and capillary vasodilatation with increased vascular permeability in the microcirculation affecting brain, lung, and other organs. Molecular mechanisms and chemical mediators involved in brain edema pathogenesis in humans are mostly unknown.

Authors' contributions
M. Adeva and G. Souto carried out the literature search and wrote the draft of the manuscript. C. Donapetry and M. Portals reviewed diabetic ketoacidosis- and salicylate poisoning- associated brain edema. Acute liver failure-related brain edema was reviewed by D. Lamas. M. Adeva and G. Souto reviewed high altitude exposure and dialysis disequilibrium syndrome, while A. Rodriguez reviewed systemic capillary leakage syndrome. All authors contributed to the final version of the manuscript and revised it for important intellectual content.

Conflicts of interest
There are no conflicts of interest.

Acknowledgement
There was no financial support.

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