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BRAIN RESEARCH

Research Report

Inflammatory mediators and blood brain barrier disruption in fatal brain edema of diabetic ketoacidosis

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ABSTRACT

Brain edema (BE) is an uncommon but life-threatening complication of severe diabetic ketoacidosis (DKA) and its treatment. Despite advances in treatment of DKA, the pathogenesis of both initiation and progression of the associated BE is unclear. In the present study we examined the blood brain barrier (BBB) integrity and the potential involvement of the inflammatory mediators in BBB breakdown in two cases of fatal BE associated with DKA. In both cases there were typical signs of disruption of the BBB manifested by the absence of tight junction proteins (occludin, claudin-5, ZO-1 and JAM-1) in the parenchymal blood vessels, as well as albumin extravasation in examined brain areas. The neuroinflammatory markers chemokine CCL2, NF-κB and nitrotyrosine were localized in the perivascular areas of the disrupted BBB and diffusely distributed in the brain parenchyma. Our data indicate that neuroinflammation plays a role in the BBB disruption of the fatal BE of DKA.

1. Introduction

Two forms of brain edema (BE) are associated with severe diabetic ketoacidosis (DKA): subclinical (asymptomatic) and clinical (symptomatic). Subclinical BE is frequently present prior to and during treatment, and usually resolves without known sequels (Durr et al., 1992; Glaser et al., 2004; Hoffman et al., 1988; Krane et al., 1985). In contrast, clinical BE is a life-threatening complication of DKA which occurs in slightly less than 1% of children with severe DKA, usually within the first 24 h following the initiation of treatment, and results in a high prevalence of morbidity and mortality (Edge et al., 2001; Glaser et al., 2001).

Several metabolic factors have been hypothesized to be mediators in subclinical and clinical BE. For example, the ketone bodies acetoacetate (AcAc) and β-hydroxybutyrate (βOHB) have been demonstrated to increase the expression of vasoactive peptides and intercellular adhesion molecule-1 (ICAM-1), and also to increase activation of the Na–K–Cl cotransporter in cerebral capillary endothelial cells (CCEC), suggesting involvement of transcellular permeability in the BE of DKA (Edge et al., 2006; Hoffman et al., 2002; Isales et al., 1999; Lam et al., 2005;

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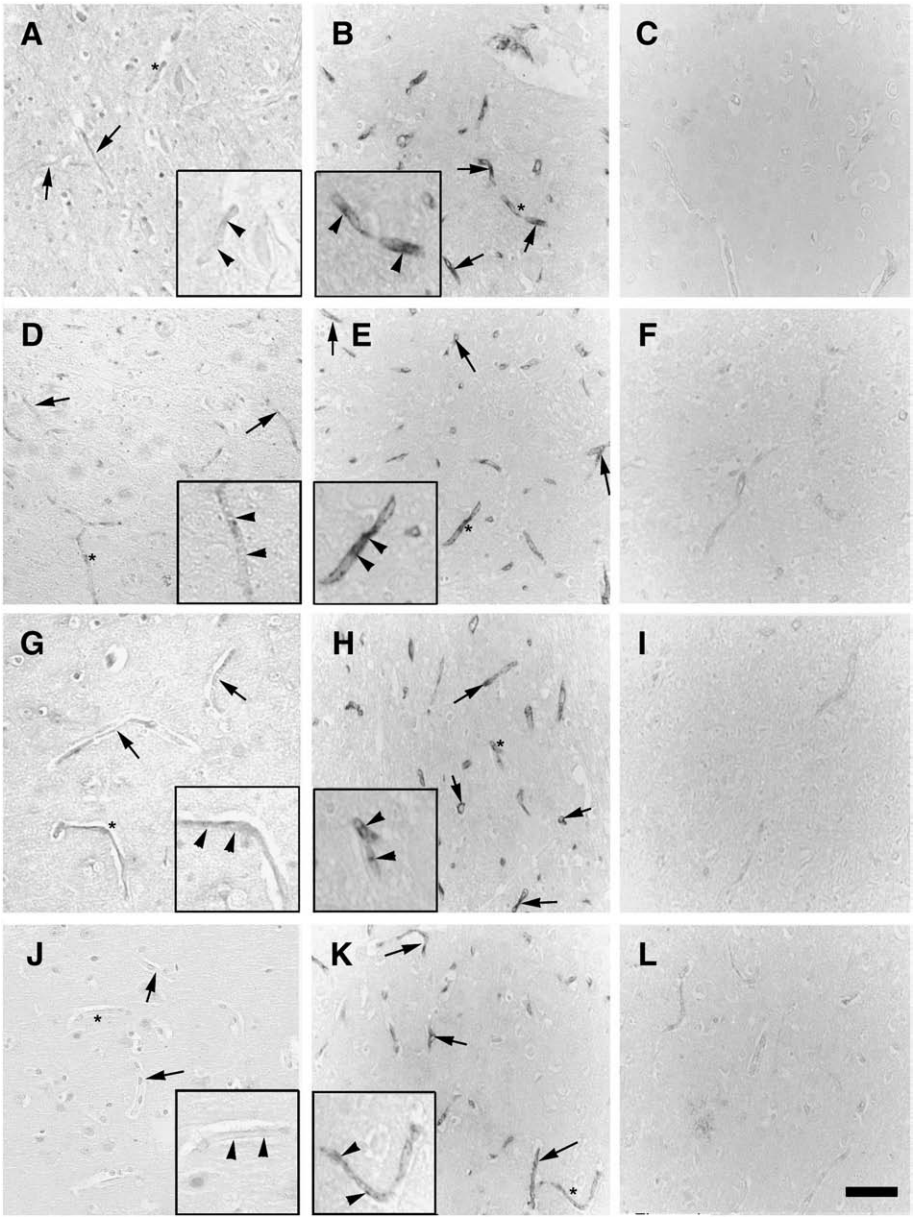

Fig. 1 – The distribution of tight junction proteins is disrupted in DKA. (A, D, G, J) In DKA sections, numerous small and medium-sized vessels exhibit decreased to absent occludin, claudin-5, ZO-1 and JAM-A immunoreactivity (arrows), (B, E, H, K) In control sections, blood vessels show strong immunoreactivity for the tight junction associated protein, occludin, claudin-5, ZO-1 and JAM-1 in a continuous, interendothelial staining pattern. C, F, I, and L are brain section stained with correspondent isotype IgG protein. Scale bar=50 μm.

Prockop, 1971; Van Der Meulen et al., 1987). Emerging candidates for the progression of BE during severe DKA are an immuno-inflammatory response and oxidative/nitrosative stress (Krizbai et al., 2005; Petty and Lo 2002). The systemic inflammatory response (SIR), involving proinflammatory cytokines and the complement cascade, is maximally increased during the time subclinical BE is progressing, as well as at the time when clinical BE is most likely to occur (Hoffman et al., 2003a, Jerath et al., 2005). Several recent studies have reported a particular association of inflammatory response with fatal BE of DKA, pinpointing: 1) a neuroinflammatory response with the generalized expression of IL-1β; 2) the receptor for advanced glycation end products (RAGE) and the membrane attack complex C5b-9 on numerous cells and the microvasculature; and 3) an intense expression of these proinflammatory mediators on the choroid plexus in the DKA cases (Hoffman et al., 2006, 2007, 2008). However, it is not known if the clinical BE that occurs in the fatal BE of DKA involves "breakdown" of the blood brain barrier (BBB) and "opening" of the paracellular route, or if it consists solely of an accentuated perturbation of the cerebral microvascular endothelial cells (CMEC).

Due to the fact that proinflammatory cytokines, C5b-9 and other proinflammatory mediators have the potential to cause an increase of BBB permeability and BBB breakdown