Review

Peritumoral Brain Edema — Pathogenesis and Therapeutic Implications —

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Abstract : Peritumoral brain edema is a significant cause of the neurological morbidity associated with brain tumors. Review of the literature on the pathogenesis of the formation of peritumoral brain edema has identified a number of biochemical and morphological abnormalities. The mainstay of medical therapy of peritumoral brain edema is systemic steroids. The mechanisms of action of steroids are reviewed and the new therapeutic modalities are discussed.

Key words : brain edema, brain tumor, steroids, blood-brain barrier

Introduction

Peritumoral brain edema is a well known complication of brain tumors¹⁾. Patients afflicted with brain tumors typically present with progressively worsening headaches, vomiting and depressed level of consciousness. All of these clinical features are clearly related to elevated intracranial pressure (ICP). Peritumoral brain edema is due to an ultrafiltrate of plasma containing water, electrolytes, and plasma proteins, that emanates from the brain tumor microvasculature. Edema fluid infiltrates the white matter surrounding a brain tumor in a diffuse manner. This excessive accumulation of edema fluid contributes to the elevation of ICP. In the clinical situation, computed tomography (CT) and magnetic resonance imaging (MRI) are very useful in the diagnosis of peritumoral brain edema. The use of gadolinium (Gd-DTPA) will increase the ability of MRI to specifically differentiate tumors from peritumoral brain edema²⁾ (Fig. 1).

Classification

In 1967 Klatzo³⁾ classified brain edema in two major categories. vasogenic and cytotoxic brain edema. Fishman⁴⁾ added the third category of interstitial brain edema.

Vasogenic brain edema is associated with marked alterations of the microvascular elements. This disturbance in the blood-brain barrier results in extravasation of plasma-like fluid into the white matter extracellular space. Vasogenic brain edema is seen clinically in the setting of brain tumor, brain abscess, intracerebral hemorrhage and malignant hypertension.

Cytotoxic brain edema is associated with an increase in intracellular water content and preferential spreading of water in the gray matter. Cytotoxic brain edema is seen clinically in the setting of cerebral ischemia or infarction, diabetic coma and hepatic encephalopathy.

Interstitial brain edema refers to an infiltration of cerebrospinal fluid (CSF) into the

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Fig. 1. MRI images of a patient with malignant lymphoma demonstrating peritumoral brain edema and tumor enhancement (a) without and (b) with Gd-DTPA

perivascular white matter. Interstitial brain edema occurs in the setting of acute hydrocephalus.

Pathogenetic Factors of Peritumoral Brain Edema

Several biochemical and morphological abnormalities are clearly associated with the genesis of peritumoral brain edema⁵⁾ (Fig. 2).

A) Tumor angiogenesis

The progressive growth of brain tumors depends on the induction of new microvessels from the host tissue; a process called angiogenesis. Several angiogenic factors have been purified. These polypeptides include basic fibroblast growth factor and acidic fibroblast growth factor, angiogenin and transforming growth factors⁶⁾. Cu ions are also important mediators of angiogenesis⁷⁻⁹⁾. The growth and survival of primary and secondary brain tumors depends on the effects of these angiogenic factors on capillary endothelial cell locomotion and proliferation, fundamental events in the formation of new tumoral capillary blood vessels.

B) Vascular permeability factor

Tumor-derived vascular permeability factor was first found to be expressed by a hepatocarcinoma which promoted the accumulation of ascites fluid¹⁰⁾. This factor was found to be a basic protein with a high affinity for immobilized heparin and a permeability-inducing potential that was three orders of magnitude greater than histamine. Primary malignant brain tumors have been shown to contain vascular permeability factor^{2, 11, 12)}.

Fig. 2. Pathogenic factors of peritumoral brain edema

C) *Eicosanoids*

A number of eicosanoids such as prostaglandin (PG) E1, PGE2 and PGF2 are known to increase microvascular permeability in non-neural tissues. A correlation has been observed between increased tissue leukotriene C4 and human peritumoral brain edema. Leukotrienes C4 and D4 are known to increase microvascular permeability¹³⁾. Indomethacin is known to decrease eicosanoid synthesis in the rat brain¹⁴⁾ and has been shown to significantly decrease the extravasation of Evans blue in the C6 astrocytoma model¹⁵⁾. Eicosanoids may also play a role in the angiogenic cascade based on the fact that ibuprofen inhibits tumor growth¹⁶⁾.

D) *Tumor plasminogen activator*

Quindlen and Bucher¹⁷⁾ reported a positive correlation between brain edema and fibrinolytic activity. Sawaya and Highsmith¹⁸⁾ also demonstrated a weak but significant correlation between the degree of peritumoral brain edema and the degree of fibrinolytic activity of the tumoral tissue, suggesting that plasminogen activator-induced fibrinolysis is partially responsible for peritumoral brain edema.

E) *Inflammatory process*

Immunohistological studies have demonstrated macrophage accumulation in and around human brain tumors associated with edema¹⁹⁾.

F) *Biogenic amines*

The role of biogenic amines in the formation of peritumoral brain edema is controversial. Some studies have suggested that deranged metabolism of monoaminergic neurotransmitters may play a role in the early development of brain edema. We found no correlation between the degree of peritumoral brain edema and biogenic amines levels in tumor tissues²⁰⁾.

G) *Oxygen free radicals*

Oxygen free radicals play a role in increased vascular permeability²¹⁾. Recent studies have suggested that tumor cells can produce superoxide radicals and that free radical scavengers such as superoxide dismutase (SOD) and catalase in tumor cells are impaired^{22, 23)}. However, SOD failed to reduce peritumoral brain edema²⁴⁾. The role played by lipid peroxidation in peritumoral brain edema is unknown.

H) *Immunological factors*

Lymphokine-activated killer cells mediate the killing of human glioma cells in vitro, but significant peritumoral brain edema has been seen as a complication of this therapy. The intravenous administration of interleukin-2 to patients with malignant gliomas results in increased peritumoral brain edema²⁵⁾. Some immunological mechanisms may induce cellular injury and alter microvascular permeability.

I) *Morphological abnormality*

Several features of tumor-associated vascular endothelium, such as widened intercellular junctions, discontinuous tight junctions, membrane fenestrations, noncontinuous basement membranes, active micropinocytosis and paucity of mitochondria, contrast sharply with the normal architecture of the blood-brain barrier^{26, 27)}.

Treatment

There is no question that steroids are effective in reducing peritumoral brain edema both experimentally and clinically. Several possible mechanisms for this effect that have been discussed include barrier permeability, metabolic effects, vascular effects, oncolytic effects, CSF reduction and biochemical events (Fig. 3). However, steroids have not been shown to

Fig. 3. Effects of steroids on peritumoral brain edema²⁸⁾

be effective in human cerebral trauma, cerebral infarction or cerebral hemorrhage. The prolonged use of high-dose steroid therapy is associated with adverse reactions such as steroid myopathy, aseptic bone necrosis, osteoporosis, peptic ulcers, poor wound healing, onset of a cushingoid state and impairment of the immune system. Therefore alternative methods are needed to ameliorate peritumoral brain edema. Recently we have demonstrated that local delivery of dexamethasone resulted in reduction of peritumoral brain edema and a significant increase in survival time²⁸⁾. Human corticotropin-releasing factor decreased peritumoral brain edema, with fewer of the major side effects encountered with long-term, high-dose steroid therapy²⁹⁾. Ibuprofen and indomethacin had been shown to be effective in reducing peritumoral brain edema^{30,31)}. The mechanisms by which ibuprofen may decrease Evans blue extravasation in experimental models or improve brain tumor patient symptoms are unknown. A number of mechanisms could be suggested including modulation of endothelial permeability of tumor microvessels, modulation of endothelial permeability in peritumoral tissue, an influence on inflammatory cell-mediated permeability on tissue injury, a direct influence of eicosanoid inhibition on cell function and alterations in flow in tumor or peritumoral tissue secondary to prostaglandin inhibition⁵⁾.

Conclusion

The mechanism of peritumoral brain edema may be multifactorial. It is hoped that an expanded understanding of the mechanisms responsible for the genesis of peritumoral brain edema will ultimately facilitate more effective therapeutic interventions.

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