

# Mechanisms of tumor-related brain edema

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✓Cerebral edema contributes strongly to symptoms associated with brain tumors. Although the introduction of corticosteroids has greatly simplified treatment of patients with newly diagnosed tumors, these drugs are associated with marked side effects during the long-term treatment that is often necessary in the recurrences. Therefore, a better understanding of mechanisms related to the evolution and clearance of tumor-related edema with the aid of modern imaging and molecular methodology is clearly necessary. Recently, researchers have focused on molecular mechanisms of edema development and have demonstrated alternative routes—such as the inhibition of vascular endothelial growth factor receptor inhibitors—to be explored for treating edema. In this review the author focuses on established and current concepts regarding the pathophysiology of cerebral edema and its treatment.

**KEY WORDS** • brain tumor • morphology • pathophysiology • therapy • vasogenic edema

**E**DEMA ASSOCIATED WITH brain tumors plays a major role in determining symptoms caused by cerebral tumors.<sup>70</sup> Not only does edema cause additional mass effect, often exceeding the mass induced by the tumor itself and resulting in increased intracranial pressure, it also leads to neurological disturbances by disrupting tissue homeostasis and reducing local blood flow.<sup>27,51,91</sup> Nearly all focal lesions, including primary and metastatic tumors, abscesses, encephalitides, and radionecroses, produce vasogenic edema. Although steroids have facilitated the management of edema in patients with newly diagnosed brain tumors, long-term therapy of tumor-associated edema remains an important issue in the context of recurrent malignant gliomas or lesions treated using radiosurgery or radiotherapy rather than resection. Nevertheless, authors of only a few studies have specifically addressed clinical management issues of cerebral edema. Furthermore, viewing tumor-associated edema as a single entity is probably not justified. For example, in contrast to edema surrounding metastases (Fig. 1) or meningiomas, peritumoral edema associated with high-grade gliomas (Fig. 2) is characterized by extensive infiltration of tumor cells. Types of peritumoral edema may therefore be distinguishable, depending on histopathological and clinical properties. Adopting a more differentiated view would likely lead to improved strategies of treatment and diagnosis for brain tumors accompanied by peritumoral edema.

*Abbreviations used in this paper:* BBB = blood-brain barrier; COX-2 = cyclooxygenase-2; CT = computed tomography; DT = diffusion tensor; GBM = glioblastoma multiforme; MR = magnetic resonance; NO = nitric oxide; NOS = NO synthase; VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor; WHO = World Health Organization.

In this review I summarize the established and new concepts regarding the pathophysiology of peritumoral edema based on morphological and molecular findings, as well as modern imaging.

## Capillary Ultrastructure in Brain Tumors

Edema associated with brain tumors is considered to be vasogenic and thus pathophysiologically similar to edema due to brain injury or cerebral abscesses. The primary disturbance is at the level of the microvasculature.<sup>50</sup> In simplified terms, the tight junctions that form the BBB protect the brain's interstitial space from plasma extravasation under normal conditions, as there is no lymphatic system within the brain. In vasogenic edema, vascular permeability is increased. Under normal conditions a "sink effect" is provided by the ventricles and subarachnoid cerebrospinal fluid to allow steady circulation and replenishment of the extracellular space. This sink effect is overwhelmed in vasogenic edema, resulting in extracellular fluid accumulation.

Edema resulting from tumors must be distinguished from cytotoxic edema, for instance as a consequence of hypoxia of cytotoxic origin, resulting from cellular swelling after breakdown of transmembraneous ion gradients due to energy depletion.<sup>40,50</sup> These two types of brain edema were first differentiated by Klatzo<sup>38</sup> in the 1960s.

Metastatic and nonglial brain tumors produce angiogenic factors that promote capillary formations with marked ultrastructural abnormalities. In nonglial brain tumors, pinocytotic vesicles are observed more frequently, and the basal laminae are more irregular.<sup>80</sup> Glial tumors also lack a normal BBB. In a spheroid model of glioma in

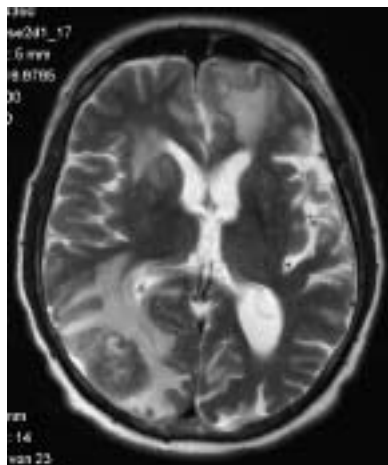


FIG. 1. Axial T2-weighted MR image showing the typical aspect of edema in cerebral metastases in a patient with pulmonary carcinoma.

rats, the mass of tumor vessels display either abnormal tight junctions or fenestrations.<sup>86</sup> In human gliomas endothelial cell junctions of capillaries appear either short or elongated, and the endothelia display hyperplasia, surface infolding of endothelial cells, irregular basal laminae, and large extravascular spaces in ultrathin and freeze-fracture replicas.<sup>80</sup> Proliferated endothelia in malignant gliomas are further characterized by fenestrations, defective tight junctions, increased numbers of pinocytotic vesicles, and incomplete ensheathment of endothelial cells by the basal membrane. Although vascular permeability cannot be measured directly in tumor specimens from humans, it can be inferred that tumor vessels—which are derived from previously existing vessels—demonstrate structural abnormalities that explain their lost barrier functions, allowing leakage of plasma exudate into the surrounding brain.<sup>28,44,45,55</sup>

On a molecular level, morphologically disrupted tight junctions in newly formed brain tumor capillaries are associated with a paucity or lack of proteins such as occludin, claudins, or the junctional adhesion molecule. These entities are all part of the molecular composition of tight junctions in the healthy brain.<sup>15,18,19,29,52,64</sup> These transmembrane proteins bind intracellular proteins such as ZO-1 and ZO-2. Binding results in the coupling of tight junctions to the cytoskeleton of endothelial cells. It has been suggested that a decrease in expression or function of these tight junction proteins leads to opening of the junction and to the formation of edema. This hypothesis is supported by findings from several studies. For example, only low levels of claudin-1 were found to be expressed in microvessels from GBM, whereas high-grade gliomas (WHO Grades III and IV) did not express functional occludin.<sup>42,64</sup>

### The Role of VEGF

In addition to structurally abnormal tumor vessels within the tumor itself, the vessels in neighboring tumor tissue may be affected by infiltrating tumor cells and show clear ultrastructural changes, such as elongated junctional clefts (unfused regions) and an increase in the density of en-

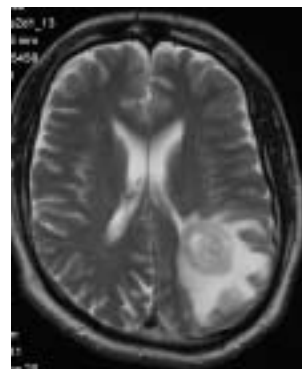


FIG. 2. Axial T2-weighted MR image showing cerebral edema in a patient with GBM.

dothelial vesicles, depending on the density of infiltrating cells. These changes were also observed when vessels were not immediately invested by tumor cells, suggesting the presence of cytokines, which spread into peritumoral tissue and disrupt normal vascular morphology.<sup>85</sup>

One cytokine that has been under close investigation is VEGF. Paracrine signal pathways involving VEGF may be involved in the generation of peritumoral edema. This cytokine was originally described as vascular permeability factor and is involved in angiogenesis and vascular permeability.<sup>78</sup> The VEGF binds to endothelial cells via the tyrosine kinase receptors flt-1 (VEGFR-1) and Flk-1/KDR (VEGFR-2). Both are predominantly expressed on endothelial cells.<sup>16,56</sup> Vascular endothelial growth factor appears to be involved in tumorigenesis, neovascularization, and edema production.<sup>48</sup> Apart from its mitogenic and chemotactic influence on endothelial cells, VEGF potentially enhances permeability of endothelium and is approximately 1000 times more potent than histamine.<sup>12,13</sup> Similar to histamines and other mediators, VEGF exerts its effects on venules and small capillaries and acts immediately on endothelial cells, but not on smooth muscle cells, fibroblasts, or neutrophils, through mobilization of intracellular calcium.<sup>48</sup> Vascular endothelial growth factor may impair the function of occludin by phosphorylation of this protein, with consecutive opening of tight junctions.<sup>63</sup> Possibly, VEGF induces fenestration of the endothelium and enhances capillary permeability through this mechanism.<sup>72</sup> On the other hand, upregulation of VEGF has been observed in brain tumors commonly associated with edema, such as GBMs, meningiomas, and metastases.<sup>7,61,65,88</sup> In patients with meningioma, there is a correlation between the presence or absence of peritumoral edema and levels of VEGF mRNA.<sup>22,37</sup> Meningiomas with pronounced edema displayed higher levels of VEGF protein staining.<sup>68</sup>

Nevertheless, in the clinical situation clear correlations between VEGF and brain tumor grade or prognosis are missing.<sup>48</sup> Therefore, the presence of edema does not automatically imply a high grade of malignancy. For example, secretory meningiomas are benign meningiomas (WHO Grade I) and display extensive edema surrounding the tumor.<sup>61,65,75</sup> Meningiomas are not considered severely hypoxic, and other factors that upregulate VEGF may be involved, such as platelet-derived growth factor, epidermal growth factor, and estrogens.<sup>48,53,83</sup> Edema in menin-

gliomas has also been associated with morphological factors, including tumor size and histological subtype, whereby transitional and meningotheliomatous types tend to produce more edema.<sup>21</sup> Furthermore, invasion of adjacent brain by meningioma has been related to the presence of edema.<sup>8,32,49</sup> The invading meningioma phenotype disrupts the bordering arachnoid, possibly providing a route for the spread of edema mediators, including VEGF. These mediators may cause not only the propagation of edema but also the proliferation of new blood vessels, thus explaining the high correlation between pial blood supply and peritumoral brain edema.

In contrast, VEGF expression in human gliomas is related to their degree of malignancy. Low-grade gliomas express low levels of VEGF, whereas progression of low-grade gliomas into malignant gliomas is associated with an up to 50-fold increase in VEGF mRNA levels.<sup>66</sup> Increased VEGF expression has been correlated with vascular permeability *in situ*.<sup>46</sup> The expression of VEGF is largely restricted to perinecrotic cells, suggesting that hypoxia regulates its expression in high-grade gliomas.<sup>82</sup> Conversely, pilocytic astrocytomas (WHO Grade I) have an excellent prognosis while displaying high levels of VEGF mRNA.<sup>41</sup> Regulation of VEGF in these tumors may be the consequence of factors other than hypoxia, such as a loss of function of the p53 tumor suppressor gene.<sup>58</sup>

### Other Mechanisms Under Investigation

Apart from VEGF, other factors implicated in edema formation related to brain tumors include arachidonic acid metabolites and NO. Elevated levels of leukotriene C4 (produced via the lipoxygenase pathway) have been found in GBM and in adjacent edematous brain tissue in correlation with the amount of peritumoral edema.<sup>9,59</sup> In a rat glioma model, microglia, which infiltrates brain tumors, was demonstrated to be a major source of prostaglandin E2 production through the COX-2 pathway.<sup>3</sup> The COX-2- and lipoxygenase-derived biologically active lipid mediators are thought to promote tumorigenesis and peritumoral brain edema.<sup>59</sup>

Nitric oxide has been identified as a specific mediator of vasodilation and tumor blood flow in primary brain tumors and has also been investigated in the context of brain tumor-associated edema. The concept involves induction of NOS isoenzymes as a result of tumor hypoxia. Inducible NOS II is expressed in tumor-infiltrating microglia and macrophages. However, a correlation between the quantity and expression of NOS has not been demonstrated in primary brain tumors, whereas a specific edema-modulating role of NO in cerebral metastasis has been considered.<sup>10</sup> In this context, it appears that VEGF-induced edema formation may occur via the synthesis and release of NO.<sup>54</sup> Other vasogenic substances that may contribute to the pathophysiology of tumor-related edema are serotonin, thromboxanes, and platelet-activating factor.<sup>20,30</sup>

Macrophages may also be involved in edema accumulation because the degree of macrophage infiltration seen on immunoperoxidase staining correlates with the extent of peritumoral edema.<sup>81</sup> This has been taken to suggest that secretory products of macrophages might contribute to edema formation associated with brain tumors.

An additional hypothesis with possible implications for the formation and regulation of brain edema has recently emerged after the discovery of the aquaporin protein family. Aquaporins are small, hydrophobic, integral membrane proteins that are expressed in all living organisms and play critical roles in controlling the water flow into and out of cells. In the brain, aquaporin-4 is expressed in endothelial astrocytic foot processes. Aquaporin-4 is highly upregulated in high-grade gliomas.<sup>60,74</sup> As yet, however, it is undetermined whether this upregulation results in increased edema formation or in enhanced clearance of edema. Nevertheless, modulation of the expression and/or function of aquaporins may provide novel therapeutic options for reducing brain tumor-associated edema.

### Bulk Flow of Edema

One of the first pathophysiological aspects of tumor-associated edema to be studied extensively was bulk flow. Interest in bulk flow has recently been revived due to the development of convection-enhanced delivery as a treatment modality for malignant gliomas, as well as to advances in neuroradiology, such as DT imaging. Historically, the introduction of CT in the 1970s advanced the understanding of edema propagation and resolution in patients. Around that time it was established that tumor-associated edema propagates by bulk flow rather than by simple diffusion. Due to bulk flow, small pressure gradients, such as the gradient between gray and white matter, are sufficient to prevent or redirect the spreading of edema. White matter has a lower resistance than the more densely packed gray matter; therefore, edema tends to propagate in fingerlike projections throughout the white matter.<sup>69</sup> This phenomenon has been confirmed with mathematical models based on CT measurements.<sup>1</sup> Computed tomography has also been used to measure the speed of extravasation of intravenous contrast material.<sup>34</sup> Based on a spherical model of edema propagation from the lesion, the formation rate of edema fluid was calculated as 0.5 to 3.2 ml/hour and the speed of edema fluid spreading to 1.9 mm/hour. In a patient with a metastasis, fluid was produced at a rate of 3.9 ml/hour, which led to an edematous volume in the brain of 87.3 ml.<sup>70</sup>

In these key analyses it was recognized that the volume of edema depends not only on the rate of edema production but also on the rate of resorption of extravasated fluid. Clearance of extravasated fluid was considered to be due to the hydrostatic pressure responsible for the bulk flow of edema fluid pushing the fluid away from the lesion until it is cleared primarily in the ventricular<sup>71</sup> and, to a lesser extent, the subarachnoid cerebrospinal fluid.<sup>95</sup> Other clearance mechanisms include absorption through the subarachnoid space, which has been demonstrated to be independent of intracranial pressure<sup>95</sup> or—to a limited extent—the resorption of extravasated proteins by astrocytic cells. This mechanism decreases the extracellular oncotic pressure and thus limits propagation, contributing to the resolution of edema.<sup>24</sup> Finally, there is a limited amount of absorption by local capillaries in the edematous tissue, which can be quantified (authors of one study found this rate to be 0.0086 ml/hr/cm<sup>3</sup>).<sup>24</sup> Work involving edema formation and resolution before and after dexamethasone treatment has shown that the drug acts by de-

creasing edema formation rather than by increasing its resolution.<sup>33</sup>

The more recent emergence of MR imaging as a diagnostic tool has corroborated the earlier CT findings and has given access to additional information regarding the pathophysiology of tumor-related edema. For instance, by measuring changes in relaxation time (T1), the extracellular distribution volume ( $V_e$ ) and capillary permeability expressed as the unidirectional transport rate constant ( $K_i$ ) can be calculated for various tumor types. Meningiomas have a higher  $K_i$  than gliomas or metastases. After treatment with dexamethasone, the  $K_i$  decreases by 52% in gliomas and metastases, but only by 4% in meningiomas.<sup>2</sup> Magnetic resonance imaging has also been used to measure cerebral blood flow, cerebral blood volume, and brain-tumor barrier permeability. Changes in perfusion have been studied using dynamic perfusion-weighted MR imaging. Relative regional cerebral blood volume and flow were almost 50% lower in peritumoral brain edema than in the contralateral white matter in patients with meningiomas.<sup>91</sup> Furthermore, the positive effects of dexamethasone administration on cerebral blood flow and BBB permeability have been quantified by MR imaging.<sup>4,62</sup>

More novel assessments of peritumoral edema involve DT imaging for making visible and analyzing apparent water diffusivity in tissues *in vivo*.<sup>5,39,57</sup> Using this technique, investigators have found greater apparent water diffusivity in high-grade gliomas, whereas the anisotropy (the property of being directionally dependent) in these lesions was comparable to that of edema in other tumors (low-grade gliomas, metastases, and meningiomas). This observation was taken to imply that there are two distinct types of peritumoral edema: edema associated with high-grade gliomas and edema associated with low-grade gliomas or nonglial tumors, despite the lack of a signal intensity difference between these two edema groups on T2-weighted MR imaging. Water movement in areas of edema, predominantly in the extracellular spaces, was less restricted in high-grade gliomas, a phenomenon that likely reflected the destruction of the extracellular matrix ultrastructure by malignant cell infiltration and, consequently, greater water diffusion. On the basis of these observations, it has been argued that DT imaging could be used as a clinical tool for differentiating high-grade gliomas and for evaluating the extent of cellular infiltration.

Correlative studies on the histopathological characteristics of malignant gliomas and imaging findings have demonstrated a high degree of concordance between the T2 signal abnormality on MR images as an indicator of edema and tumor cell infiltration.<sup>93</sup> Fractional anisotropy seen on DT images correlated with the density of tumor cell infiltration.<sup>84</sup> Therefore, a strong association between edema propagation and malignant cell infiltration has been shown in these studies.

This understanding of cell migration and fluid flow dynamics within tumor and brain interstitial space has gained attention in the context of convection-enhanced delivery, which has been developed as a novel instrument for transporting drugs to infiltrating malignant glioma cells.<sup>25</sup> Therefore, methods of assessment and visualization of fluid movements within the brain, such as DT imaging, will be of future interest, not only for optimizing edema treatment, but also for optimizing brain tumor therapy.<sup>76</sup>

## Management of Brain Tumor Edema

The mainstay of therapy of brain tumor-related edema is corticosteroids for both nonglial and glial tumors. These drugs have been used since the 1960s<sup>36,73</sup> and have led to a remarkable decline in perioperative mortality and morbidity rates. The preferred compound is dexamethasone due to its low mineralocorticoid effects in comparison with other corticosteroids. With long-term use, however, the positive action is counterweighted by deleterious side effects such as immunosuppression, weight gain, gastrointestinal problems, osteoporosis, myopathy, and an enhanced risk of deep vein thrombosis and pulmonary embolism. The mechanisms of action of corticosteroids are still unclear. Corticosteroids lead to a decrease in the rate of edema formation without effecting clearance,<sup>33</sup> which appears to occur within 1 hour after administration, as demonstrated by reductions in capillary permeability.<sup>79</sup> Although data have been presented showing that dexamethasone acts by reducing the expression of VEGF,<sup>26,47</sup> this agent may act by interfering with VEGF action on the target endothelial cell.<sup>55</sup> In cultured endothelial cells, VEGF has been shown to increase intracellular  $Ca^{2+}$ , which has been associated with cytoskeletal rearrangement. Dexamethasone appears to block this influx.<sup>14</sup> Furthermore, in peripheral blood vessels, the increase in vascular permeability seen after intradermal injection of VEGF is inhibited by systemic administration of dexamethasone, acting through the glucocorticoid receptor.<sup>11,26</sup>

In Western Europe, neurooncologists try to treat brain tumor-induced edema and to overcome corticosteroid dependency as well as corticosteroid-related side effects by administering boswellic acids (H15). These are phytotherapeutic agents that are believed to inhibit edema formation and even tumor growth in patients with malignant gliomas.<sup>35,87</sup>

A number of additional experimental approaches are being pursued at the moment; some are still in the pre-clinical stage, and some are in early clinical studies. Thrombin has been investigated as a possible target of antiedema strategies. An enzyme involved in the coagulation cascade, thrombin has also been implicated in brain edema formation, angiogenesis, and cell proliferation. Argatroban, a thrombin antagonist, was shown to reduce edema, tumor growth, and tumor-related neurological deficits in rat glioma models.<sup>23,31</sup>

Attention has also been directed toward corticotropin-releasing factor, a polypeptide that regulates adrenocorticotropin hormone release from the pituitary gland, which in turn regulates hydrocortisone secretion from the adrenal gland. Corticotropin-releasing factor has also been studied in conjunction with intracerebral gliomas and has been found to reduce BBB permeability in a tumor model<sup>90</sup> and to improve neurological function in patients suffering brain metastasis.<sup>92</sup>

Due to its implication in the generation of brain tumor-related edema, selective inhibition of VEGF has been explored, for instance by the antiangiogenic drug SU5416 (semaxanib), a small molecule that selectively inhibits tyrosine kinase activity of the VEGFR Flk-1/KDR. This drug has been associated with prolonged survival in rats with intracerebral gliosarcoma and increased necrosis while reducing vascularity.<sup>89</sup> Similar observations

were made in nude mice with human GBM xenografts.<sup>77</sup> Although promising activity in neoplastic disease outside the brain has been demonstrated in patients,<sup>17,43,96</sup> the value of semaxanib in brain edema treatment is unclear. On the other hand, the pan-VEGFR inhibitor AZD2171 has to date shown efficacy in normalizing vasculature and alleviating edema in patients with GBM,<sup>6</sup> giving proof of the principle of this concept and endorsing further studies.

Another class of compounds has recently received some attention, the inhibitors of COX2. In one study, the COX-2 inhibitor SC-236 has demonstrated a prolongation of survival similar to dexamethasone when administered in rats with intracerebral gliosarcomas.<sup>67</sup> Similarly, the diffusion of contrast medium into adjacent brain was attenuated in rats with intracerebral C6-gliomas after pre-treatment with rofecoxib, another selective COX-2 inhibitor. Rofecoxib was as effective as dexamethasone in these experiments. A mode of action for COX-2 inhibitors might be the reduction of transcription factor Sp1's DNA binding and transactivating activity, resulting in less production of VEGF.<sup>94</sup>

### Future Directions

To date, VEGFR antagonists, COX-2 inhibitors, boswellic acid, and other experimental therapeutic agents have not been shown to be superior to corticosteroids in the management of brain tumor-related edema; furthermore, careful assessments are required. A better understanding of different types of tumor edema related to different pathological entities and their molecular mechanisms may open the way to targeted therapies. Improved understanding of the molecular mechanisms controlling BBB permeability will allow manipulation of this permeability for improving therapy for malignant brain tumors with drugs that, under physiological circumstances, cannot cross this important barrier.

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