

Pathogenesis of peri-tumoral edema in intracranial meningiomas

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Abstract Peri-tumoral edema in intracranial meningiomas occurs frequently and obviously impacts the morbidity and mortality of these predominantly benign neoplasms. Several causative factors (age, gender, volume, location...) have been unsuccessfully investigated. Despite recent progresses in metabolic imaging and molecular biology, the pathogenesis of peri-tumoral edema remains debated. Hypotheses include vascular endothelial growth factor, metalloproteinases and interleukins among many others. It is probable that this pathogenesis encompasses all these factors with different levels. The current review aims to shed the light on the investigated factors involved in the pathogenesis of peri-tumoral edema in meningiomas and identify the potential therapeutic targets.

Keywords Meningioma · Peri-tumoral brain edema · Vasogenic edema · Cytotoxic edema · Vascular endothelial growth factor · Metalloproteinases · Aquaporins · Interleukins · Mast cells · Hypoxia-inducible factor

Abbreviations

PTBE	Peri-tumoral brain edema
BBB	Blood-brain barrier
VEGF	Vascular endothelial growth factor
BNP	Brain natriuretic peptide
AQP	Aquaporin
MMP	Metalloproteinases
HIF	Hypoxia-inducible factor
IL	Interleukin
WHO	World Health Organization

Introduction

Meningiomas are the second most frequent intracranial neoplasm following gliomas. They represent about one fifth of intracranial neoplasms [26, 102]. Eighty-five percent of these occur in the supratentorial compartment [114]. Female to male ratio reaches 2:1 [114]. Meningiomas are classified into three types in the WHO classification: benign (80% and 9 histological subtypes), atypical (15 to 20% and 3 subtypes), and anaplastic (1 to 3% and 3 subtypes) [112]. Gross total resection still remains the gold standard treatment, while radiotherapy and radiosurgery play a significant role in the management either as primary treatment or following surgery.

The occurrence of peri-tumoral brain edema (PTBE) is not rare in intracranial meningiomas, except for suprasellar locations, affecting between 38 and 67% of patients harboring an intracranial meningioma [39, 45]. This PTBE may raise the morbidity and mortality [3, 31, 136] by increasing brain shift and intracranial pressure [79], making the surgical removal challenging and it also is a predisposing factor to perioperative epilepsy [70, 139]. Moreover PTBE has been associated with a higher risk of postoperative intracranial hematoma [126] as

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well as neurological deficits [1, 139]. The pathogenesis of PTBE in meningiomas is still unclear and implicates to varying degrees *inter alia* vascular endothelial growth factor A (VEGF-A) [50, 75, 85, 109, 121], aquaporin 4 [65, 88, 129, 142], and matrix metalloproteinase 9 (MMP-9) [50, 92, 94]. During the last two decades, main studies have focused on the molecular characteristics of meningiomas through research concerning signal transduction pathways. It is now well established that meningiomas express receptors for epidermal growth factor [55, 64], dopamine [21, 137], platelet-derived growth factor [124], prolactin [82], and somatostatin [101]. In contrast relatively little is known about the role of extracellular matrix and PTBE in tumor-associated angiogenesis, invasion, cell signaling, and migration.

We herein review the pathogenesis of the PTBE as some specific treatments may relieve this edema prior to the meningioma's treatment and therefore impact morbidity and mortality as well. A better understanding of this pathogenesis will probably open new insights into targeted therapies in meningiomas.

Methods

A bibliographic search until June 2016 via Medline, Scencedirect, and Scopus databases was performed with the keywords “meningioma,” “peri-tumoral brain edema,” “VEGF,” “matrix metalloproteinase,” and “aquaporin.” The abstracts of identified publications were reviewed and only relevant papers were considered excluding case reports. There were no language restrictions.

Clinical evidence

Up to 67% of intracranial meningiomas harbor a certain amount of peri-tumoral edema [45]. Several studies attempted to correlate PTBE with various clinical and pathological factors including sex, age, tumor location, tumor size, histological subtypes, and venous obstruction. None of these correlations was statistically significant and definitely conclusive.

No study demonstrated any correlation or trend regarding sex and age. Concerning the impact of the volume of the meningioma, there is a trend toward a greater incidence of PTBE in larger tumors. In Bitzer et al. study, the incidence of PTBE was 20.7% in tumors inferior to 10 ml in contrast to an incidence of 92.3% of PTBE in tumors larger than 10 ml [12]. This trend was also reported significantly in other studies confirming the hypothesis that a larger surface of brain compressed by the tumor volume leads to more frequent hypoxic consequences and brain/tumor adhesion issues [122].

Other studies reported the correlation between a shorter course of the symptoms reflecting a rapid growth of the tumor, and the incidence and importance of PTBE [128]. Even if

supratentorial locations were thought to be more generative of PTBE, the majority of studies dealing with location as a specific factor of PTBE revealed that suprasellar meningiomas were quite never associated with PTBE, probably because of the multiple arachnoid layers in this region.

Bitzer et al. and de Vries et al. noted a significant correlation between WHO grade II and III meningiomas and a more extensive PTBE [12, 140]. Elsewhere, a specific subtype of meningiomas, known as secretory meningiomas, is commonly associated with very large PTBE [103], as well as microcystic and angiomatous patterns.

In a recent series of 61 patients with benign meningiomas, Simis et al. noted that the extent of PTBE in meningiomas had a positive correlation with the presence of irregular margins of the tumor and higher recurrence rates, as well as with a larger volume of the meningioma on the basis of a bivariate analysis [125]. The authors conclude that larger meningiomas may disrupt the arachnoid membrane leading to leakage of edemogenic factors in the adjacent brain. Multivariate analysis confirmed the association between PTBE and the volume of the meningioma and revealed a correlation between the extent of PTBE and the risk of seizures. In the same paper, Simis et al. verified the existence of a positive statistical correlation between an irregular shape and the extent of PTBE, reinforcing the hypothesis that an irregular interface brain/meningioma favors brain invasion and edema development [39, 71, 84, 122]. In their prospective series of 135 patients that underwent total removal of intracranial meningiomas, Mantle et al. [77] noted a correlation between the extent of PTBE and the recurrence risk, as did Simis et al. Nakano et al. found that hyperintense meningiomas on T2WI were frequently accompanied by large PTBE, probably because of the larger water content of these tumors [83].

In fine, there is no clear cut positive correlation between any clinical, histological, or imaging factor and the existence of PTBE, but there is a trend toward the development of marked PTBE in large meningiomas (except for secretory, microcystic, and angiomatous histological subtypes), those developing on the supratentorial convexity particularly the middle fossa, those with irregular margins, and those with a marked pial vascular recruitment.

Pathogenesis

The pathogenesis of PTBE still remains subject to debate. Historically, Klatzo classified cerebral edema as vasogenic and cytotoxic types [61–63]. He defined vasogenic edema as secondary to an increase of capillary permeability, resulting in protein and fluid extravasations into the extracellular space particularly into the white matter. The gray matter is theoretically spared because of its intricately woven cellular architecture limiting considerably the free movement of fluids in the

extracellular space. In contrast, during cytotoxic edema, the fluid is accumulated in the intracellular compartment mainly within the glial cells including the gray matter. Four main theories on PTBE pathogenesis can be individualized:

- The brain parenchyma compression theory: Tumor size may play an important role in the genesis of PTBE. Large meningiomas lead to compression, ischemia, and cytotoxic edema [36, 39, 76]. This theory cannot be generalized as sometimes very small meningiomas cause extensive PTBE. There was no clear significant correlation between tumor size and the importance of edema in many recent case series [47, 68, 76, 93] (Fig. 1a, b). According to this theory, the incidence of PTBE in large meningiomas occurring in the elderly should be lower than in the general population of patients with intracranial meningiomas because of age-related brain atrophy, but even this statement has not been statistically demonstrated.
- The secretory-excretory theory: Some specific histological subtypes of meningiomas, particularly secretory ones [105], produce eosinophilic and periodic acid-Schiff (PAS) positive inclusions secreted along the perivascular spaces and therefore generate PTBE mainly through an osmotic mechanism [2, 18, 19, 127]. Although secretory meningiomas are usually surrounded by extensive PTBE [141], the frequency of this histological subtype (less than 3% of all meningiomas) cannot explain the overall incidence of PTBE in meningiomas [103] (Fig. 2a–c).
- The venous compression theory: Tumoral obstruction of veins and sinuses hinder the venous outflow around the meningioma. This theory was not clearly proven in large angiographic series even if in specific cases venous obstruction may represent an aggravating factor [10, 11].
- The hydrodynamic theory: The concept of intra-tumoral congestion. Tanaka et al. in 2006 found a significant relationship between PTBE and hypoplastic efferent tumoral veins using superselective angiography [130]. The

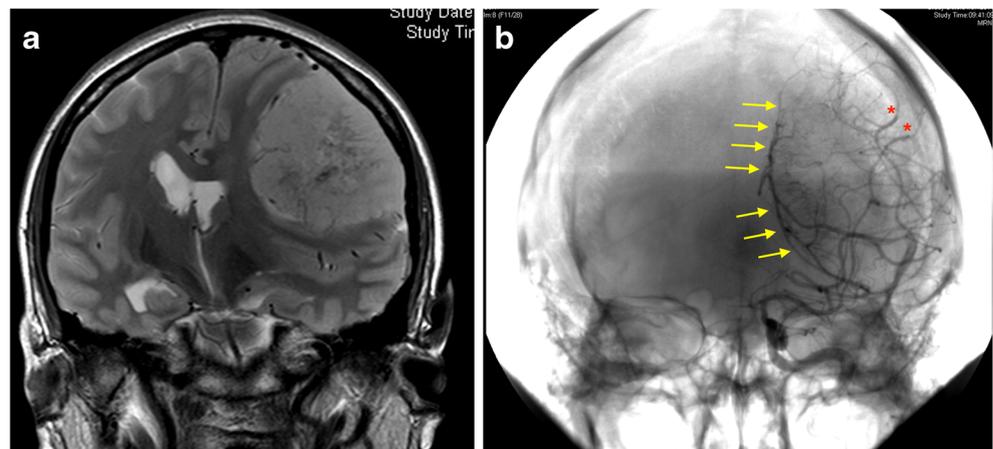
hydrodynamic theory states that when tumoral blood supply becomes insufficient, meningiomas secrete angiogenic factors resulting in immature highly permeable neovessels and therefore to leakage of plasma proteins within the tumor [85, 86]. These angiogenic factors include mainly VEGF-A but also endothelin-1 and caveolin-1 [4, 123, 146]. If the meningioma-brain interface is permeable (absence of arachnoid interface), these angiogenic factors diffuse in the surrounding brain parenchyma and vasogenic substances lead to the development of PTBE [30]. Similarities between peri-tumoral edema in meningiomas and experimentally induced vasogenic edema have been noted, reinforcing this vasogenic theory [36].

Angiogenesis, vascular permeability, and inflammation

Role of vascular endothelial growth factor

Initially described as vascular permeability factors (VPF), vascular endothelial growth factors (VEGF) are key polypeptides regulators of vessel formation during embryogenesis and in wound healing as well as vessel homeostasis. Different variants of VEGF have been recently described, but the most studied remains VEGF-A which activates numerous signaling pathways through VEGF receptor-2 and modulates vessels morphogenesis through VEGF receptor-1 with the help of various factors such as platelet-derived growth factors, angiopoietins, transforming growth factor beta, and basic fibroblast growth factor [7, 52, 54, 97]. During the first stages of angiogenesis, VEGF modulates vascular dilation, vascular leakage, and endothelial cell formation while during the late stages it regulates maturation and stabilization [8, 40, 146]. VEGF connects to endothelial cells via two receptors, the tyrosine kinase receptors flt-1 (VEGFR-1) and Flk-1KDR (VEGFR-2), both widely expressed on endothelial cells.

Fig. 1 Left hemispheric convexity grade II meningioma (**a** coronal T2WI and **b** coronal left internal carotid angiogram). Very minimal peri-tumoral edema is noted despite the WHO histological grade and the extent of pial arterial vessels recruitment from the left middle cerebral arteries (arrows). The meningeal arterial feeding is commonly assured by branches of the middle meningeal artery (*)



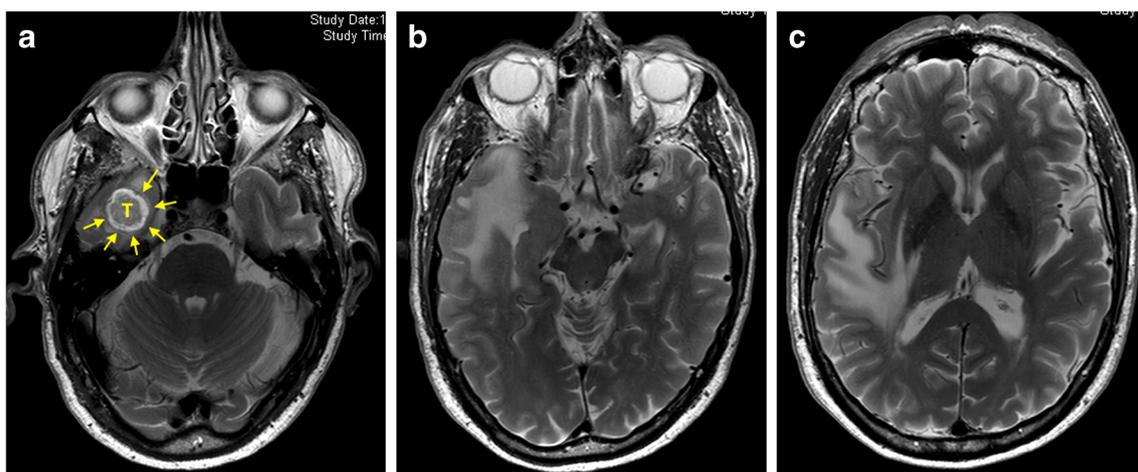


Fig. 2 Right temporal fossa secretory meningioma generating extensive temporo-parietal edema (a–c axial T2WI). Note the meningioma (T) is very well demarcated from the adjacent temporal lobe (arrows) (a)

Concerning the development of peri-tumoral brain edema in meningiomas, VEGF is thought to play a major role both in the regulation of vascular permeability (by opening of tight junctions through a phosphorylation of occludin) and the modulation of angiogenesis [74, 90, 98, 123]. In addition to other growth factors that induce VEGF secretion (epidermal growth factor, basic fibroblast growth factor), hypoxia is a powerful stimulator of VEGF secretion [9, 138]. In meningiomas, VEGF is synthesized both in tumoral cells and in the endothelium of tumor vessels [33], but not produced directly within the peri-tumoral matrix [30]. Meningiomas displaying intense VEGF immunostaining presented with a higher peritumoral edema incidence and edema index than in meningiomas VEGF-negative [9, 40, 58]. As a corollary, a high VEGF expression associated with the presence of a large PTBE has been proposed as predictors of recurrence in low-grade meningiomas [77, 145]. Nassehi [86] found peri-tumoral edema in 43/101 meningiomas with a statistically significant correlation with VEGF expression, as confirmed by Hou et al. and Markovic et al. [45, 78, 85]. In addition to PTBE, the tumor size and its proliferative index is correlated with VEGF expression. Dharmalingam et al. noted that 65% of grade I meningiomas displayed VEGF expression in contrast to 100% of grades II and III [28]. Markovic et al. studied the influence of the severity of PTBE and the intensity of expression of VEGF on morbidity and mortality, noting that the treatment outcome was significantly better when VEGF expression was below 50%. In the same study, the postoperative complications were more frequent in the group with PTBE, as well as the longer duration of intensive care treatment [78]. The vascular pattern of meningiomas has also been linked to VEGF expression: Pistolesi et al. identified small microvessel architecture in grade II and III meningiomas with a high VEGF expression in contrast to few larger vessels in grade I meningiomas with lower VEGF expression [99]. This data suggest that vascular architecture can also constitute a prognostic factor. Finally,

other growth factors have been investigated unsuccessfully in their possible correlation with PTBE in meningiomas such as VEGF-B, scatter factor/hepatocyte growth factor, placenta growth factor, and fibroblast growth factor-2 [66].

Mast cells, hypoxia-inducible factor-1 (HIF-1) and meningiomas

Meningiomas can be infiltrated by a variety of cells, predominantly of the immune environment such as mast cells, macrophages, and CD8 lymphocytes [15, 115]. This raises the question whether this represents an innate immune reaction toward the tumor itself or constitutes a growth environment participating to the tumorigenesis process [100]. A few authors reported a possible correlation between meningioma grade and the presence of mast cells, but the results are unclear [51, 107, 108]. The role of mast cells in the growth of meningiomas has also been suggested [37, 110]. Mast cells are multi-effector cells originating from a bone marrow progenitor. They participate to allergic reactions, immunity either innate or adaptative, inflammatory processes and autoimmunity as well. These cells have been described in various locations particularly within the central nervous system particularly choroid plexuses, meninges, hypothalamus, pituitary stalk, and pineal gland [29, 133]. Reszec et al. evaluated mast cells in a series of meningiomas using tryptase immunostaining [107, 108]. Meningiomas were classified in two groups: low grade including WHO grade I, and high grade encompassing WHO grades II and III. In this study, 31.8% of low-grade meningiomas displayed mast cells all of them presenting with marked PTBE, while 86% of high-grade meningiomas were positive for mast cells with 100% PTBE. Mast cells were found in the perivascular spaces but also within the tumor tissue. In their second study, Reszec et al. evaluated the expression of HIF-1 in addition to mast cells [108]. HIF-1 is a transcriptional factor that may, under

hypoxic conditions, induce the transcription of different genes implicated in tumor angiogenesis, invasion, cell survival, and glucose metabolism [53]. Overexpression of HIF-1 has been shown in various cancers to be correlated to grade and tumoral progression including in glioblastomas [108]. Tryptase expression which reflects the presence of mast cells was observed in 40.4% of grade I meningiomas and in 90% of high-grade meningiomas (WHO grades II and III) while HIF-1 was present in 55.7% of low grade and in 84% of high-grade meningiomas [108]. In this recent study, the presence of PTBE statistically correlated with tryptase and HIF-1 expression. The authors suggested that hypoxia generates mast cell activation and HIF-1 overexpression leading to blood-brain barrier rupture and therefore PTBE. In another study, Tirakotai et al. found that secretory meningiomas (WHO grade I), known to produce large PTBE, are highly infiltrated by mast cells [134]. The same findings were observed in chordoid meningiomas (WHO grade II) [34, 132]. Mast cells may also play a role in the cystic changes observed in one out of ten meningiomas [100]. Finally, it has been hypothesized that mast cells may be implicated in the pathogenesis of headaches associated with small meningiomas, secondary to interactions between meningeal mast cells and neurons [43].

Interpretation of tenascin expression

In meningiomas, the expression of different angiogenic factors has been demonstrated: platelet-derived growth factor, VEGF and fibroblast growth factor-2 [13, 14, 66]. Interactions between these factors within the extracellular matrix in the immediate environment of the tumor involve other key molecules. Tenascin is an extracellular matrix glycoprotein involved in embryogenesis, wound healing and tumor-associated angiogenesis [20, 59, 69, 96]. It is now established that there is a strong relationship between tenascin expression and tumoral angiogenesis [25, 73]. Indeed tenascin stimulates the proliferation and the motility of endothelial cells [147]. Kilic et al. established that there is a clear correlation between tenascin expression and VEGF expression in meningioma hypothesizing that tenascin may be a nonspecific angiogenic matrix molecule directly involved in meningioma angiogenesis [59]. The latter study showed also a correlation between tenascin expression and PTBE in meningiomas: among the 12 meningiomas not expressing tenascin 6 showed absent or minimal edema and 6 moderate edema, while of the 13 meningiomas with moderate tenascin expression, 9 showed marked PTBE [59]. Kilic et al. suggested that tenascin not only plays the role of an extracellular matrix modulating adhesion, migration and proliferation of endothelial and meningioma cells, but also participates to the process of brain invasion by the meningioma [59].

Influence of matrix metalloproteinases

Matrix metalloproteinases (MMP) are proteolytic enzymes involved in the degradation of extracellular matrix constituent, and are part of the physiological process of tissue remodeling. Among these, MMP-9 appears to be involved in tumor invasion process and angiogenesis [5, 50, 109]. MMP-9 is able to degrade the architecture of the extracellular matrix including the basement membrane and can interfere in the MAP kinase pathway resulting in the activation of cell proliferation. In meningiomas, intra-tumoral expression of MMP-9 seems to correlate with PTBE [28, 42, 46] and cell proliferation [5, 22]. Reszec et al. showed significant expression of MMP-9 in both low- and high-grade meningiomas but a clear trend toward significant expression in atypical, recurrent and malignant meningiomas was observed [109]. In this study, all meningiomas presenting with PTBE strongly expressed MMP-9. Jung et al. confirmed that MMP-9 levels were significantly associated with the intensity of PTBE [57]. It has been also noted that MMP-9 expression was directly related to VEGF expression and pial blood supply of meningiomas, through disruption of the surrounding arachnoid membrane [50]. The role of MMP-9 has been demonstrated in microcystic meningiomas: PTBE is frequently associated with this subtype and MMP-9 expression is very high. Paek et al. confirmed that an increased ratio of MMP-9 to TIMP-1 (tissue inhibitors of matrix metalloproteinases) might be associated with a microcystic degeneration of the meningioma and the formation of PTBE [94]. Nevertheless, other studies did not confirm these findings. In a canine study of intracranial meningiomas, Beltran et al. did not find any statistically significant relationship between MMP-9 and MMP-2 expression and the severity of PTBE [6].

Role of interleukine-6

Interleukin-6 (IL-6) is a multifunctional cytokine with stimulatory effects on immune response. It has been identified as a B cell differentiating factor but it is also involved as a mediator of inflammation, cellular differentiation, and immune response [35, 60, 131]. An increased expression of IL-6 in the brain has been noted in various situations including HIV-encephalopathy, multiple sclerosis, and Alzheimer disease [41, 44]. An overexpression has also been demonstrated in glioblastomas as a promoter of autocrine growth, pituitary adenomas, and meningiomas [16, 23, 135]. The role of IL-6 in meningiomas is still debated as it may act as a growth stimulator in approximately 60% of meningiomas whereas it can act as an inhibitor of tumor cell proliferation as well [17, 56, 135]. Outside the central nervous system, IL-6 is associated with local edema formation by induction of inflammation and an increase in capillary permeability, particularly in pulmonary edema [91, 113]. Par et al. found that IL-6 mRNA expression was more than 7 times higher in the moderate-to-severe peri-

meningioma edema than in those without or with very limited edema [95]. The mechanism of action of IL-6 is not clear but it appears to influence directly the integrity of the blood-brain barrier and may induce changes in the morphology and permeability of endothelial cells [80, 120]. In addition, IL-6 can simulate other substances involved in the pathogenesis of perimeningioma edema such as VEGF and MMP-9 [11, 122].

Involvement of E-cadherin and beta-catenin

E-cadherin is an epithelial Ca^{2+} -dependent cell adhesion molecule that plays a primordial role in embryonic development and morphogenesis. This molecule can be detected in epithelial tissues and cancers as well as in arachnoid villi and meningiomas. Beta-catenin is a multifunctional protein that interacts directly with E-cadherin forming the E-cadherin/catenin complex, a component of the adherens junction and an indirect modulator of tumoral cell signaling and proliferation [27, 49]. Changes of the tumor suppressor gene E-cadherin (CDH1) may play a significant role in the determination of meningioma aggressiveness and the severity of PTBE. Zhou et al. showed that the expression levels of E-cadherin and beta-catenin decreased significantly when the meningioma grade increased to reach almost null values in malignant meningiomas [148]. These authors noted a correlation between the expression levels of these molecules and the extent of PTBE and hypothesized that the harm of the cell-to-cell junctions damages the tumor-brain interface, facilitating the invasion of the adjacent brain by meningioma cells.

Role of water-electrolyte balance regulation

Aquaporins

Aquaporins are a group of 14 water channel proteins. These small size membrane-spanning proteins are expressed at plasma membranes in various tissues including brain parenchyma, particularly aquaporins 1, 4 and 9 in the latter location. Specifically, aquaporin 4 is predominantly expressed in the peri-vascular astrocytic foot processes and is suspected to be involved in the pathogenesis of chronic hydrocephalus and brain edema. Elsewhere in normal baseline conditions, aquaporin 4 may be involved in the clearance mechanism of the interstitial brain compartment also known as the glymphatic system. Recent studies have shown that an increased expression of aquaporin 4 is associated with PTBE in meningiomas [88, 142]. The inhibition of these water channel proteins may be a therapeutic option in the multimodal management of edematous meningiomas. More recently aquaporin 5 (AQP5) has been investigated. Lambert et al. showed that AQP5 is expressed in meningiomas, with a role in cerebral water homeostasis but also in tumor cell proliferation, opening

new research pathways for recurrent or inoperable meningiomas [65].

Brain natriuretic peptide (BNP)

The heart ventricles as a consequence of left ventricle stretching secrete the brain natriuretic peptide (BNP) intended to maintain hydro-electrolytic homeostasis by downregulating the sympathetic nervous system as well as the renin-angiotensin loop, increasing smooth muscle relaxation and peripheral vascular resistance, and stimulating natriuresis. The level of BNP in the plasma is used routinely in the clinical practice as a marker of heart failure but also renal failure or hypoxia. BNP receptors have been found throughout the central nervous system and BNP level in the plasma suggested as a brain injury marker [143]. This level has also been correlated to the mass effect caused by brain tumors or brain edema in stroke [81, 118, 119]. Recently, Ruggieri et al. demonstrated that serum BNP levels are positively correlated to the volume of PTBE in patients with brain tumors [119]. Their prospective observational study integrated 110 patients including 40.9% of meningiomas, 30% of gliomas and 29.1% of metastases. The level of serum BNP seems to be directly related to the amount of PTBE rather than to the volume of the tumor itself. This brain source of BNP should not be confounded with the cardiac source that may complicate some neurological acute conditions mainly subarachnoid hemorrhages known as Takotsubo syndrome [89]. The mechanism of this phenomenon is still debated and whether BNP is only an epiphenomenon of peri-tumoral brain edema or participates to its production is still questioned. Therefore, Ruggieri et al. added PTBE to the list of known factors associated with high levels of serum BNP, i.e., gender, body mass index and intracranial pressure. They also proposed the serum level of BNP in patients with brain tumors as an indicator for the selection of patients who would more benefit from anti-edematous therapies (steroids, mannitol, diuretics) [119].

Influence of the brain-meningioma interface

As meningiomas are usually well-circumscribed extra-axial tumors, there is often a clear plane composed of connective tissues (pia-arachnoid mater and tumor stroma) that theoretically may limit the influence of intra-tumoral factors (VEGF, MMP...) on the adjacent peri-tumoral brain (Fig. 3a–c). Therefore the study of this interface and particularly the identification of the factors that may disrupt this interface are of paramount importance in the understanding of the pathogenesis of PTBE. Nakasu et al. studied 50 surgical cases of meningiomas [84]. They identified 20 cases with an individualized capsule categorized as thin ($n = 13$) and thick ($n = 7$). None of the atypical or anaplastic meningiomas displayed a

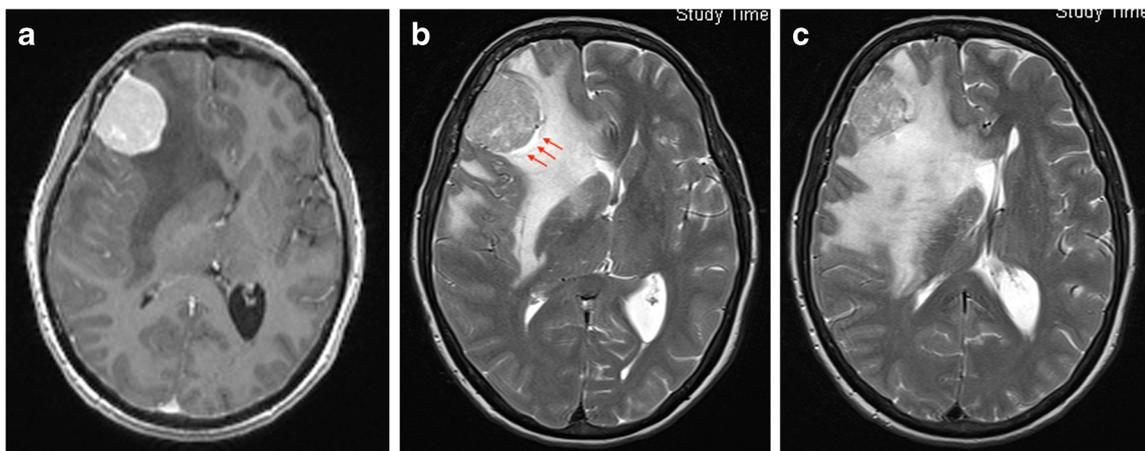


Fig. 3 Right frontal convexity grade I meningioma with extensive hemispheric edema. Note the apparent hyperintense rim surrounding the tumor that may suggest a clear plane of cleavage, in a patient presenting with status epilepticus (**a** axial T1WI with gadolinium and **b**, **c** axial T2WI)

capsule. They did not note any correlation between the extent of PTBE and the capsule thickness. Nevertheless and surprisingly, 6/7 of benign meningiomas with a thick capsule displayed PTBE whereas 5/13 thin-capsule meningiomas and 6/20 no-capsule meningiomas harbored PTBE. They concluded that the thick capsule significantly correlated with the extent of PTBE ($P = 0.024$). In this same study, the authors showed a clear correlation between PTBE and arachnoid disruption, and pial blood supply confirming the hypotheses of previous studies. Data including those of previous studies did not prove the positive correlation between MMP expression, particularly MMP-2 and MMP-9, and neither the disruption of the brain-tumor interface nor the brain invasion [50, 92, 94, 109].

Multimodal imaging of PTBE in meningiomas

Recent imaging studies explored the possibilities of characterization of PTBE in brain tumors in general and meningiomas in particular to determinate the nature of edema as vasogenic and/or cytotoxic. Except ongoing works involving hybrid PET-MR, the noteworthy studies used proton magnetic resonance spectroscopy ($^1\text{H-MRS}$) [24, 32]. The most significant modifications in the PTBE were a decrease of N-acetylaspartate (NAA) content and a frequent lactate peak [111]. Chernov et al. reported that the severity of metabolic abnormalities in the PTBE depends upon three interrelated factors: tumor growth and invasive patterns, extensive PTBE, and large volume of the meningioma [24]. The disruption of the arachnoid and pial membrane around the meningioma leads to the direct influence of active substances like VEGF-A and MMP-9 stimulating the pial vasculature and thus vasogenic edema. This is also accompanied by ischemic alterations resulting from the direct compression of the adjacent brain from large tumors. The reduction of NAA reflects

the neuronal dysfunction and cell loss. The decrease of choline may reflect the destruction of astrocytes in the PTBE whereas the lactate peak results from ischemic changes. A precise metabolic characterization of the PTBE may predict the clinical presentation and potential sequelae. Indeed, Kamada et al. demonstrated strong correlations between the residual motor functions and NAA/choline and lactates/choline ratios. Further studies involving PET/MRI may better characterize PTBE and predict the risk of definitive neurological sequelae or epilepsy when ischemic changes are predominant. The role of elastography and specific MR sequences (such as brain surface motion imaging—BMSI) is still under investigation [106, 144]. These sequences appear promising for the exploration of the complex interactions between the meningioma and the surrounding brain parenchyma.

Management of PTBE in meningiomas

Steroids remain the most frequently used agents for the management of PTBE in intra- and extra-axial intracranial tumors including meningiomas. The widespread use of synthetic steroids since the mid-1950s such as prednisone and dexamethasone, known to have a potent glucocorticoid activity, have shown an outstanding and prompt efficacy on vasogenic edema [48]. The possibilities of oral use and one daily administration facilitated this use in clinical practice. Nevertheless, the use of steroids, particularly long-term, can be associated with a noteworthy toxicity including hyperglycemia, arterial hypertension, osteoporosis, myopathy, psychiatric disorders (insomnia, mood disorders and psychosis), thromboembolic events as well as immunosuppression. In edematous forms of meningiomas, steroids may be administered perioperatively beginning a few days before surgery. Steroids are thought to modulate the permeability of the blood-brain barrier frequently altered by various cytokines such as VEGF. This modulation is assured

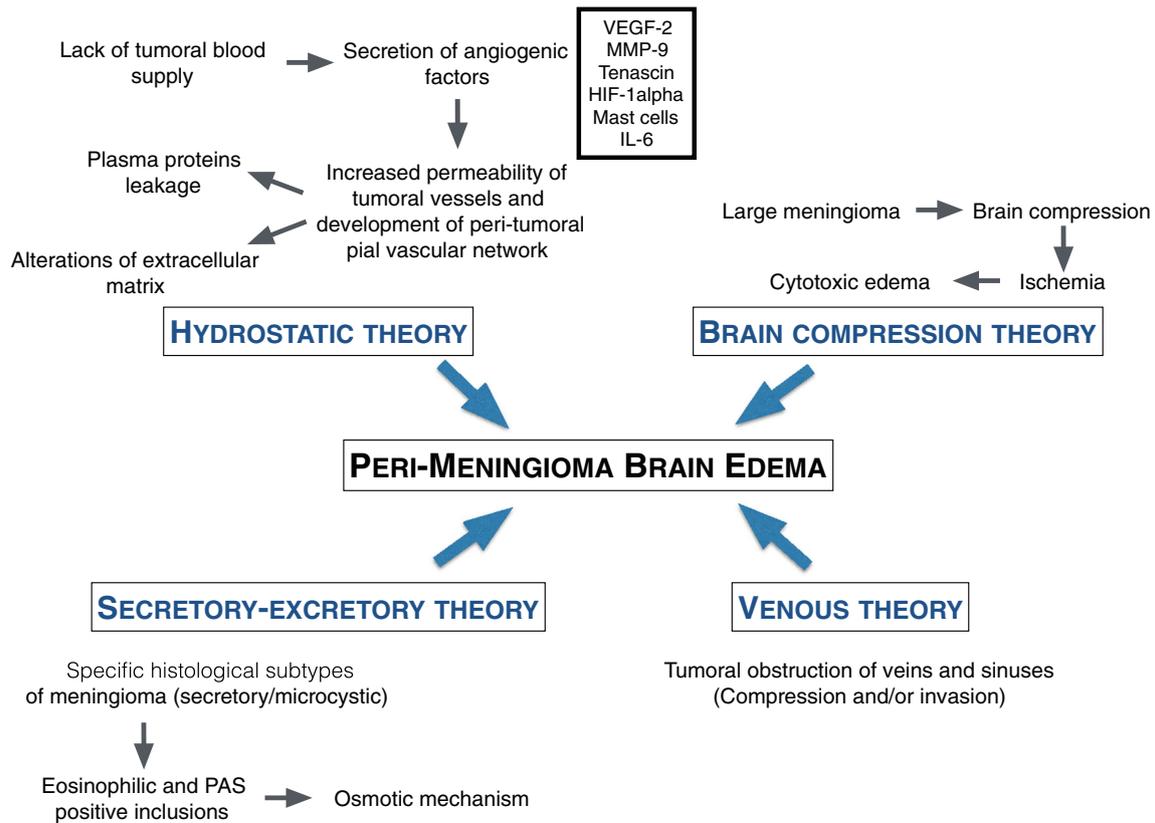


Fig. 4 Theories on the pathogenesis of PTBE in intracranial meningiomas. *VEGF* vascular endothelial factor, *MMP* metalloproteinase, *HIF* hypoxia-inducible factor, *PAS* periodic acid-Schiff

through different mechanisms involving claudins, zona occludens (ZO)-1, vascular endothelial-cadherin, and occludin [116, 117]. Limitations of steroid treatment are the risk of impairment in the quality of life because of potentially serious side

effects and the transitory anti-edematous effect. Other agents may be used in the daily practice especially if steroids are contraindicated, such as mannitol and hypertonic saline but which are associated with a risk of electrolytic disturbances.

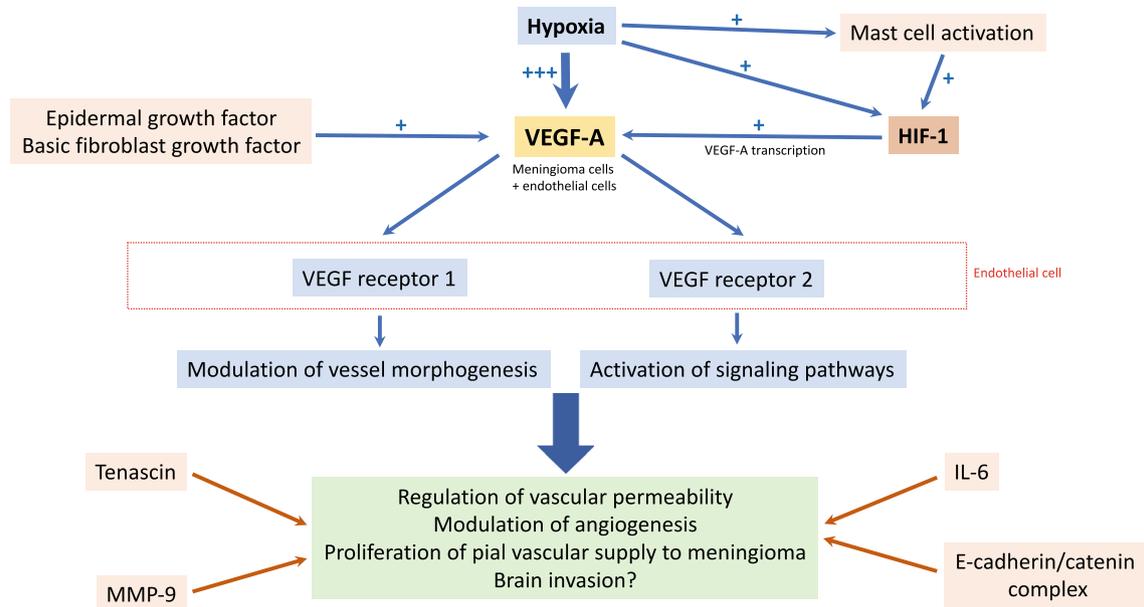


Fig. 5 Summary of the interrelated molecular mechanisms highlighting the role of hypoxia in the genesis of PTBE in intracranial meningiomas. *VEGF* vascular endothelial factor, *MMP* metalloproteinase, *HIF* hypoxia-inducible factor, *IL* interleukine

Elsewhere, corticotropin-releasing factor (CRF) appears to significantly reduce PTBE by a direct action on CRF-1 and CRF-2 receptors on blood vessels. More recently, studies on the effect of cyclooxygenase-2 inhibitors appear interesting despite cardiologic risks [38].

Future research pathways

VEGF remains one of the most studied targets in neurooncology as it concerns various neoplasms. Very rare studies have involved a VEGF-directed therapy in meningiomas [42, 67]. Bevacizumab is a humanized monoclonal antibody that inhibits VEGF activity by binding to VEGF and inhibits VEGF receptor binding, thereby preventing the growth and maintenance of tumor blood vessels. Puchner et al. published the first report using bevacizumab in an anaplastic meningioma [104]. It was used as a salvage therapy after the recurrence of anaplastic meningioma following gross total removal and radiotherapy, with a partial remission. Rare studies involving meningiomas followed with similar results. Interestingly, one of these reported by Nayak et al. in addition to the stability or shrinkage of the enhancing tumor, 40% of patients exhibited a significant reduction of PTBE [87]. Even though the published data is very limited concerning the anti-tumoral and anti-edemagenic activities of bevacizumab in meningiomas, a trend toward efficacy exists. Various ongoing trials using hydroxyurea, temozolomide, bevacizumab, interferon-alpha, irinotecan, imatinib, tamoxifen, mifepristone and octreotide for recurrent and anaplastic meningiomas revealed a median PFS ranging from 2 to 15 months [45, 72]. PTBE as evaluated on T2WI on MRI decreased by 40% with a clinical benefit in all these cases. The association of everolimus, a mammalian target of rapamycin inhibitor, in anaplastic and recurrent meningiomas is being evaluated. In selected patients with severe PTBE, targeted treatments may help improve the perioperative morbidity.

Conclusion

The accurate comprehension of the multifarious pathogenesis of PTBE in meningiomas is of paramount importance as the extent and severity of edema may impact the neurological outcome. Obviously, none of these different hypotheses can explain by itself the genesis of PTBE; this latter may result from a conjunction of the different mechanisms (Fig. 4). The concept of a purely extra-axial tumor has to be revisited taking into account the interaction with the peri-tumoral brain tissue through the production of VEGF, metalloproteinases, pial irrigation development, and extracellular matrix reorganization (Fig. 5). Future trials of targeted treatments directed ideally

toward both meningioma proliferation and surrounding edema are expected.

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Compliance with ethical standards

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