Role of hydrodynamic processes in the pathogenesis of peritumoral brain edema in meningiomas

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Object. In a prospective study, 28 patients with 32 intracranial meningiomas were examined to determine the role of hydrodynamic interaction between tumor and surrounding brain tissue in the pathogenesis of peritumoral brain edema. Methods. Gadolinium–diethylenetriamine pentaacetic acid (Gd-DPTA), an extracellular contrast agent used for routine clinical imaging, remains strictly extracellular without crossing an intact blood–brain barrier. Therefore, it is well suited for investigations of hydrodynamic extracellular mechanisms in the development of brain edema. Spin-echo T₁-weighted magnetic resonance images were acquired before and after intravenous administration of 0.2 mmol/kg Gd-DPTA. Additional T₁-weighted imaging was performed 0.6, 3.5, and 6.5 hours later. No significant Gd-DPTA diffused from tumor into peritumoral brain tissue in 12 meningiomas without surrounding brain edema. In contrast, in 17 of 20 meningiomas with surrounding edema, contrast agent in peritumoral brain tissue was detectable after 3.5 hours and 6.5 hours. In three of 20 meningiomas with minimum surrounding edema (< 5 cm³), contrast agent effusion was absent. After 3.5 hours and 6.5 hours strong correlations of edema volume and the maximum distance of contrast spread from the tumor margin into adjacent brain parenchyma (r = 0.84 and r = 0.87, respectively, p < 0.0001) indicated faster effusion in larger areas of edema. Conclusions. The results of this study show that significant contrast agent effusion from the extracellular space of the tumor into the interstitium of the peritumoral brain tissue is only found in meningiomas with surrounding edema. This supports the hypothesis that hydrodynamic processes play an essential role in the pathogenesis of peritumoral brain edema in meningiomas.

KEY WORDS • meningioma • brain edema • arachnoidea • bulk flow

In contrast to what is known about intraaxial tumors, the pathophysicsiology of the generation of edema surrounding meningiomas is not well understood. Meningiomas are primarily extraaxial tumors, physically separated by the leptomeninges from the brain. The arachnoid mater, the subarachnoid space, and the pia mater as well as the cerebral cortex represent the anatomical barriers protecting the brain from edema associated with meningiomas. Despite this, brain edema is present in approximately 60% of all cases involving meningiomas.6,20

Due to the continuing uncertainty surrounding the pathogenesis of the generation of edema associated with meningiomas, various hypotheses have been proposed: 1) ischemia caused mechanically by tumor compression;14 2) stasis induced by tumor in venous drainage areas followed by venous congestion;15 3) excretory–secretory phenomenon in which substances produced by tumor appear in adjacent brain tissue that then induces edema;22 and 4) hydrodynamic processes whereby extravasates from meningiomas appear in the surrounding brain tissue, for which leptomeningeal disintegration represents a prerequisite.17

Gadolinium–DPTA, an extracellular contrast agent given intravenously before routine clinical imaging, is distributed within the extracellular space throughout the entire body except for the CNS, where the intact blood–brain barrier prevents its crossing into the interstitium of the brain. Due to the extraaxial localization and absence of such a functional barrier in meningiomas, diffusion of this contrast medium from the intravascular into the interstitial space can be observed after the first passage.35

To understand the development of edema associated with meningiomas it is essential to determine if a quantifiable exchange of fluids between the extracellular space of these tumors and the brain occurs and whether this relates to the incidence of edema. The role of hydrodynamic processes in the pathogenesis of peritumoral brain edema associated with meningiomas was investigated using the extracellular marker Gd-DPTA in MR imaging studies.

Clinical Material and Methods

Patient Population

During the course of a prospective MR study we examined 28 patients (six men and 22 women; age range 30–79
Hydrodynamics in pathogenesis of edema surrounding brain meningiomas

years, mean 56 years) harboring 32 intracranial meningiomas. All patients were examined before any neurosurgical intervention was performed. Peritumoral edema presented in variable degrees. Patients with tumor relapses were excluded from the study. We also excluded patients in whom the tumor–brain interface in the area of edema was affected by large partial volume effects. The patients gave their informed consent prior to participating.

Table 1 shows patient characteristics and tumor data, including the locations and histological subtypes of meningiomas and the doses of steroid medication received by patients at the time MR imaging was performed. Twenty meningiomas were associated with peritumoral brain edema; edema was absent in 12 tumors. In one woman with a right-sided frontal convexity meningioma, WHO Grade II astrocytoma in the left thalamus, and a glioblastoma in the left occipital lobe were also revealed.

### Magnetic Resonance Imaging Studies

All examinations were performed using a 1.5-tesla whole body system (Magneton Vision; Siemens, Erlangen, Germany) and head coil. The imaging protocol consisted of T1-weighted spin-echo sequences (TR 630 msec, TE 12 msec, and flip angle 70˚) as well as T2-weighted turbo–spin echo sequences (TR 3000 msec, TE 14 msec, and flip angle 180˚). Slice thickness of the images acquired without gaps was 4 mm; the field-of-view was 220 × 220 mm. The spatial resolution in plane was 0.86 × 0.86 mm for T1-weighted and 0.88 × 0.86 mm for T2-weighted images. After intravenous administration of 0.2 mmol/kg Gd-DPTA, T1-weighted imaging was repeated immediately and then with delays of 0.6 ± 0.1 hours, 3.5 ± 0.4 hours, and 6.5 ± 0.6 hours with equivalent anatomical orientation.

The imaging parameters were defined as follows: pre-contrast T1-weighted images, T1ₜ₀; T1-weighted images obtained immediately after contrast injection, T1ᵣ; T1-weighted images 0.6 hours after contrast injection, T1ₜ₀.₦; T1-weighted images 3.5 hours after contrast injection, T1ₜ₀.₇; and T1-weighted images obtained 6.5 hours after contrast injection, T1ₜ₀.₉.

### Determination of Tumor and Edema Areas

On T₁ images, the borders of the meningiomas were interactively marked and the tumor area was calculated using the standard system software (Numaris; Siemens).

\[
\text{Vol} \ [\text{cm}^3] = 0.4 \ [\text{cm}] \times \sum_{e=1}^{n} \text{area} \ (e) \ [\text{cm}^2] \quad (\text{Eq. 1})
\]

where e = tumor-containing slices and area(e) = tumor area in the corresponding slice position.

The edema demarcation was demonstrated on the T₂-weighted images and the volume determined according to Equation 1.

### Evaluation of Signal Time Curves on the T₁-Weighted Images

Anatomically identical slices were compared among the series of T₁ₜ₀, T₁ᵣ, T₁ₜ₀.₇, T₁ₜ₀.₉, and T₁ₜ₀.₉ images. Representative slice positions were selected in each series.

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<th>Edema Vol (cm³)</th>
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* According to the WHO classification of meningiomas. Abbreviations: dex = dexamethasone; meningo = meningotheliomatous; NA = not available; NT = not tested; pred = prednisolone.  † Steroid dose at the time MR imaging was performed.  ‡ Intracranial part of the tumor.

Slices with relevant partial volume effects on the margins of meningiomas were excluded. Contrast-induced changes of signal intensity in the peritumoral brain tissue were evaluated based on time and distance from the tumor. Accordingly, signal profiles dependent on the distance from the tumor were measured in the selected slices of T₁ₜ₀, T₁ᵣ, T₁ₜ₀.₇, T₁ₜ₀.₉, and T₁ₜ₀.₉ images.

### Placement of the Signal Profile on Selected Axial T₁ Images

The lines were placed in those peritumoral regions that revealed an optimum representation of brain–tumor interface without relevant partial volume effects (Fig. 1 upper left). The profiles originated at the tumor margin and were placed perpendicular to the tumor surface. Depending on anatomical borders, the length of the lines varied from 10 to 26 mm to avoid crossing brain sulci. Generally, for each meningioma six profiles were acquired on the representative slices.

### Construction of an Anatomical Template

The T₁ images with the selected profile lines generated a pattern that could be superimposed on the corresponding slices in the...
Therefore, in addition to delineating the margin of the tumor and the profile lines, fixed landmarks such as the falx cerebri or the tabula interna were defined. The template could be shifted in the x–y plane when overlaid on the corresponding slices of the T1pi, T10.6pi, T13.5pi, and T16.5pi series to obtain an optimum fit to the landmarks (Fig. 1 lower left). After optimum adaptation of the template position to the corresponding images, signal values along profile lines of the pattern were evaluated at distances of 0, 1, 2, 3, 4, 6, 8, 10, 14, 18, 22, and 26 mm (Fig. 1 lower right). The signal values were determined on the lines drawn depending on the distance to tumor margin; for example, at d = 3 mm the signal value equals 437.

**Statistical Analysis**

The logarithm of six single values of SRpi, SR0.6pi, SR3.5pi, and SR6.5pi was averaged for each meningioma. Taking the logarithm of the values SRpi, SR0.6pi, SR3.5pi, and SR6.5pi allowed statistical testing against the zero value in Equation 2. The data were evaluated with a commercially available

\[
\text{SR}_{\text{pi}}(d) = \frac{S_{\text{pi}}}{S_{\text{nativ}}}(d) \times \frac{S_{\text{ref,nativ}}}{S_{\text{ref,pi}}} \quad \text{(Eq. 2)}
\]

Fig. 1. Magnetic resonance images obtained in a patient with left-sided convexity meningioma with peritumoral edema, showing signal profiles in peritumoral brain tissue. **Upper Left:** Axial T1pi image obtained immediately following administration of contrast agent. Lines placed perpendicular to the tumor surface delineate representative areas of edema. **Upper Right:** Magnetic resonance image on which a template has been constructed, marking the tumor margin, both signal profiles within edema and landmarks (tabula interna). Circular regions of interest in tumor and contralateral white matter are also seen. **Lower Left:** A T16.5pi image with identical slice position. The template was fitted to tumor margin and landmarks (tabula interna), defining the localization for signal profiles in adjacent brain parenchyma on T16.5pi images. **Lower Right:** The signal values were determined on the lines drawn depending on the distance to tumor margin; for example, at d = 3 mm the signal value equals 437.

**Fig. 2.** **Upper:** Graph showing logarithmic signal ratios from the T1pi images obtained immediately after injection of contrast agent. The geometric averages from six measurements at each distance plus standard deviations are shown. To avoid partial volume effects, a margin of 3 mm from the tumor was chosen. At d = 3 mm, signal ratios showed no significant difference from 0 (p = 0.27); thus, contrast enhancement in adjacent brain tissue was absent. **Lower:** Graph displaying logarithmic signal ratios from six measurements obtained in the T16.5pi series. Signal ratios were significantly greater than 0 up to 8 mm from the tumor margin, indicating contrast enhancement of brain tissue to that distance. At 10 mm the signal ratios were no longer significantly above 0 (p = 0.19).
Hydrodynamics in pathogenesis of edema surrounding brain meningiomas

![Graph showing incidence of contrast enhancement](image)

Fig. 3. Graphs depicting the incidence of contrast enhancement in peritumoral brain parenchyma 3 mm from the tumor margin. Upper: Graph showing frequencies to various time points for meningiomas without edema. Lower: Graph showing frequencies and time points for meningiomas with edema.

![Magnetic resonance images](image)

Fig. 4. Magnetic resonance images obtained in a patient with a right-sided frontolateral meningioma with edema and a left-sided precentral convexity meningioma without edema. a: Axial T1-weighted MR image revealing the right-sided tumor to be a secretory meningioma with voluminous white matter edema. b: Axial T1-weighted MR image obtained immediately after contrast agent injection, revealing no contrast agent extravasation into peritumoral brain tissue. c: Image obtained after 3.5 hours, revealing a marked halfmoon-shaped area of contrast agent that has spread from the tumor into the surrounding edema. d: Image revealing the tumor on the left side to be a meningotheliomatous meningioma without edema. e: Images obtained immediately after injection of contrast agent, revealing no evidence of contrast spreading. f: Image obtained immediately after injection of contrast agent, revealing no evidence of contrast agent crossing from tumor into brain tissue.

Results

Incidence of Contrast Enhancement in Peritumoral Brain Parenchyma

The incidence of contrast enhancement in peritumoral brain tissue at various time points, measured at a 3-mm distance from the tumor margin, is shown in Fig. 3. Without exception, MR imaging failed to demonstrate significant signal increases at any time in peritumoral brain parenchyma surrounding meningiomas lacking edema (Figs. 3 upper and 4d–f). In contrast, at least one of the two postimaging series in 17 of 20 meningiomas with edema revealed significant contrast enhancement (T11.5 or T14.5; Figs. 3 lower and 4a–c). Of these 17 cases in which contrast enhancement was revealed, two were seen to have significant contrast enhancement in adjacent brain tissue at 0.6 hours after contrast agent administration; signal increases were demonstrated at later times in all others. Evidence of contrast enhancement was absent in three tumors with edema in the postcontrast imaging series; however, the absolute edema volumes in these cases were less than 5 cm³. In summary, the concordance of contrast enhance-
ment in peritumoral brain parenchyma and the presence of peritumoral edema was 91% (29 of 32 tumors).

Extent of Contrast Agent Spread Into Adjacent Brain Tissue

The relationship between the maximum spread of contrast agent into peritumoral brain parenchyma and the time after contrast injection can be seen in Fig. 5. Meningiomas without edema evidenced no spread of contrast agent into the surrounding brain parenchyma (Fig. 5 upper left). Magnetic resonance imaging of meningiomas with a small amount of edema demonstrated little or no spread of Gd-DPTA into the peritumoral brain parenchyma. However, as edema volumes increased, the propensity for contrast agent to spread quickly into the surrounding brain parenchyma increased as well (Fig. 5 upper right and lower left and right). Accordingly, postimaging series performed at 3.5 and 6.5 hours after Gd-DPTA administration revealed highly significant correlations between edema volume and the maximum distance of contrast agent spreading into the peritumoral brain tissue ($r_{3.5\pi} = 0.84$, $r_{6.5\pi} = 0.87$; $p = 0.0001$).

In meningiomas with edema, contrast agent spread an average distance of $4.8 \pm 2.8$ mm in the T1$_{3.5\pi}$ series and $5.9 \pm 4.2$ mm in the T1$_{6.5\pi}$ series into the surrounding brain parenchyma.

Furthermore, there was a distinct influence of corticosteroid administration on the spread of contrast medium in peritumoral brain edema. Two patients (Cases 17 and 25) who evidenced the fastest contrast spread into peritumoral brain tissue received no or very low doses of corticosteroids (Fig. 5 lower right and Table 1). In contrast, patients (Cases 3, 9, and 12) with a small amount of brain edema in whom an absence of contrast spread was demonstrated had received corticosteroids (Fig. 5 upper right and Table 1).

Relationship Between Edema Volume and Peritumoral Contrast Enhancement

The relationship between the edema volume and the
amount of peritumoral contrast enhancement at a distance of 3 mm from the tumor margin at various time points is shown in Fig. 6.

In the T1\_pi imaging series obtained immediately after administration of Gd-DPTA, the averaged signal intensity ratios remained scattered closely around 0, independent of the edema volume (Fig. 6 upper left). As soon as 0.6 hours following injection of contrast agent, contrast enhancement was demonstrated in some meningiomas with edema, with positive trends in the signal intensity ratio (Fig. 6 upper right). However, the statistical analysis at that time point failed to yield a significant correlation (p = 0.08). The T1\_3.5pi and T1\_6.5pi series demonstrated a positive correlation between the increase in signal intensity ratio and the edema volume (r\_3.5pi = 0.86, r\_6.5pi = 0.87; Fig. 6 lower left and right) with high statistical significance (p = 0.0001).

**Signal Time Curve in Tumor Tissue**

The signal time curves within solid tumor tissue appeared fairly similar among meningiomas with and without edema. The highest signal ratios in the T1\_pi series occurred immediately after administration of contrast agent; thereafter, the signal intensity decreased exponentially over several hours. A significant difference was seen in the T1\_3.5pi series, in which there was a more prominent drop in signal noted in the tumors lacking edema compared with those with edema (log SR = 0.128 compared with log SR = 0.177, p < 0.05).

**Signal Time Curve in Cystic Tumor Areas**

Following contrast agent injection, cystic areas of tumors displayed the opposite signal pattern compared with regions of solid tumor. The T1\_pi series failed to demonstrate contrast enhancement in a patient with a cystic falx meningioma, whereas the imaging series at 3.2 hours and 5.6 hours after administration of contrast agent revealed significant increases in signal intensity within cystic areas of tumor (p = 0.0001) and simultaneous decreases in contrast enhancement in regions of solid tumor (Fig. 7). At 11.5 hours, the signal intensity within the cystic tumor areas decreased, yielding a signal time curve similar to that found in peritumoral brain tissue.

**Alterations in Signal Within Peritumoral Subarachnoid Space**

The T\_1-weighted images of the 12 meningiomas without edema were visually inspected for contrast agent spreading from the tumor into the peritumoral subarachnoid space. A ribbonlike formation of Gd-DPTA appeared within the subarachnoid space in six tumors in the post-contrast images without evidence of leakage into brain parenchyma.

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Fig. 6. Graphs showing the relationship between edema volume and degree of contrast enhancement in peritumoral brain parenchyma 3 mm from tumor margin. Graphs showing the logarithmic signal ratios obtained immediately after injection of contrast agent (upper left) and at 0.6 hours (upper right), 3.5 hours (lower left), and 6.5 hours (lower right).
the T1pi series. The areas of cystic tumor and peritumoral edema in a patient with a cystic falx meningioma. The areas of solid tumor and experimentally induced vasogenic edema.9 A disruption in the blood–brain barrier of cerebral vessels leads to a disturbance in the blood–brain barrier in the brain chyma can occur via two main mechanisms. In one process a disturbance in the blood–brain barrier in the brain tissue itself plays the primary role, whereas in the other process a disturbance in the blood–brain barrier in the brain tissue itself plays the primary role.

Because the pathogenesis remains unclear, various groups have proposed hypotheses to explain the generation of edema, including ischemic processes,24 venous congestion due to tumor compression,12 a secretory–excretory phenomenon,22 and a hydrodynamic process.10 The present study evaluated the significance of hydrodynamic mechanisms.

Gadolinium–DPTA as an Extracellular Marker

Because it is strongly hydrophilic, Gd-DPTA is unable to cross cell membranes, remaining strictly extracellular,21 without any known relevant intracellular uptake or metabolism. Furthermore, Gd-DPTA fails to traverse an intact blood–brain barrier so that after intravenous injection, this contrast medium behaves as Goldmann11 originally observed in animal experiments involving intravenous trypan blue; that is, the dye distributed itself completely throughout the extracellular space of the entire body except for the CNS. Thus, Gd-DPTA, a routinely used clinical marker for the extracellular space, reaches the entire interstitial compartment with the exception of the CNS.

Due to their extraaxial location, meningiomas are not influenced by the blood–brain barrier. The endothelial cells within these tumors demonstrate open gap junctions and endothelial fenestrations, permitting Gd-DPTA to cross fairly freely from the intravascular into the interstitial space.15 The distribution of this contrast agent into two tissue compartments is responsible for the contrast enhancement seen in meningiomas: first, the appearance of the marker within the tumor vascular system; and, second, its crossing into the extravascular interstitial space. Less than 30% of tumor contrast enhancement with iodinated contrast agents is attributable to the vascular compartment even in highly vascularized meningiomas, because the extravasation of the marker into the interstitium plays the main role.7,32,33 Because the pharmacokinetic behavior of Gd-DPTA is essentially similar to that of iodinated contrast medium, the shortening of T1 relaxation time with consecutive increase in signal intensity on T1-weighted images is primarily caused by the extravascular interstitial distribution of Gd-DPTA.

Elevated concentrations of contrast agent over several hours persist in the extracellular space of meningiomas. Thus, Gd-DPTA has sufficient time to function as an extracellular marker, spreading and accumulating in measurable concentrations in the tissue surrounding the tumor.

Discussion

Explaining the development of tumor-associated edema poses challenges because of the extraaxial location of meningiomas. Until now, the pathogenesis of this edema remained to be fully elucidated, although brain edema accompanying meningiomas has been typically attributed to a vasogenic rather than a cytotoxic origin. With the aid of an electron microscope, the appearance of edema associated with meningiomas is similar to that seen with gliomas and experimentally induced vasogenic edema.9 A disruption in the blood–brain barrier of cerebral vessels leads to the generation of vasogenic edema in glial tumors,15 permitting edema-causing plasma components to cross into the adjacent white matter. However, meningiomas grow extracerebrally, physically separated from the cerebrum primarily by the arachnoid, the subarachnoid space, and the pia mater. Part of the blood–brain barrier, the arachnoid, is impermeable to fluids. In contrast, the pia mater shows high permeability to water and electrolytes, but is far less permeable to macromolecules, such as proteins in edema fluid.10 In addition, the cerebral cortex because of its intricately interwoven cellular processes poses a structural hindrance that is almost impossible for vasogenic edema to overcome.8

Two patients harbored meningiomas in the right lateral ventricle, with the bulk of the tumor mass found in the trigon and dorsal cella media in each case. Delayed imaging revealed contrast enhancement in CSF in the right lateral ventricle. A significant signal increase proximal to the tumor in the right anterior cornu was demonstrated in one patient (3.4 hours, log SR = 0.158, p < 0.04; 6.4 hours, log SR = 0.115, p < 0.04), and in the other patient intraventricular contrast enhancement distal to the tumor in the congested right temporal cornu was demonstrated (3.6 hours, log SR = 0.260, p < 0.003; 5.3 hours, log SR = 0.235, p < 0.007).

Mechanisms of Contrast Agent Crossing Into Cerebral Tissue

This study demonstrated, after intravenous Gd-DPTA administration, contrast agent spreading from extraaxial tumor tissue into adjacent brain parenchyma in meningiomas with surrounding edema at 3.5 hours and 6.5 hours, except in three cases associated with small volumes of edema, in which the amount of contrast agent in peritumoral tissue probably fell below the level of detection.

The contrast enhancement in peritumoral brain parenchyma can occur via two main mechanisms. In one process a disturbance in the blood–brain barrier in the brain tissue itself plays the primary role, whereas in the other...
Hydrodynamics in pathogenesis of edema surrounding brain meningiomas

contrast agent spreads from the extracellular space of the tumor into the surrounding white matter.

Several pieces of evidence support the hypothesis that the extravasated contrast agent found in brain tissue originated from tumor rather than as a consequence of a disruption in the cerebral blood–brain barrier. First, the moving edge of the contrast agent advances in a wavelike manner over time from the tumor margin into the adjacent brain parenchyma. Second, leakage of contrast medium into brain tissue because of a compromised blood–brain barrier typically appears after the first pass of the marker through the cerebrovascular system, as demonstrated in perfusion studies on intraxial tumors with known barrier disruptions. Following the rapid signal decay and subsequent increase due to the intravascular passage, a significant contrast enhancement plateau persists after the first bolus pass in cases of blood–brain barrier disturbances. These phenomena, confounding for perfusion studies, originate primarily from extravasated Gd-DPTA and recirculation processes to a lesser extent. Thus, areas with compromised barrier function are usually already evident on the earliest contrast-enhanced T1-weighted images during routine neuroradiological examinations. Typically, the signal intensity drops exponentially after the first images (T1, series) and usually falls below the initial value at 30 minutes postinjection.

Even in the case of disseminated encephalomyelitis, in which a disruption in the blood–brain barrier is frequently associated with slightly delayed contrast enhancement, the maximum signal intensity is generally reached within 30 minutes. On the contrary, the time and progression of spreading of Gd-DPTA into cerebral tissue from meningiomas with edema proved completely variable. On the T1rho and T1060 images immediately after contrast agent injection, spreading of the marker into the surrounding brain tissue remained undetected except in three cases. The maximum contrast agent spreading in this study occurred generally at 3.5 hours postinjection, indicating a process that proceeded far more slowly than the typical cerebral blood–brain barrier disturbance.

Third, in the case of a cystic meningioma the spreading of contrast agent from the solid into the cystic part of the tumor could be documented. Likewise, this study demonstrated in two intraventricular meningiomas the movement of contrast medium from the tumor into the ventricular system. In all three cases, the advancement of Gd-DPTA into peritumoral brain parenchyma occurred simultaneously with contrast enhancement within the cystic portion of the tumor and the ventricular system.

Fourth, based on immunohistochemical studies on secretory meningiomas, increased vascular permeability within the tumor itself could be shown in the presence of an intact, functional blood–brain barrier within the vessels of peritumoral cortex.

Additional authors have reported that increased permeability occurred only within the tumor itself rather than in peritumoral edema in neoplasms originating from brain parenchyma.

All criteria confirm unequivocally that the time-delayed, peritumoral contrast enhancement demonstrates the movement of Gd-DPTA from the extracellular space of meningiomas into the interstitium of the brain parenchyma and that this movement cannot be attributed to a disruption in the blood–brain barrier in brain tissue adjacent to the tumor. This phenomenon offers a model for the transfer of other substances from the tumor into the surrounding white matter and substantiates that hydrodynamic processes represent the key pathogenetic mechanism by which edema develops surrounding meningiomas. Contrast agent spreading into brain parenchyma indicates leptomeningeal disintegration.

Within the leptomeninges, the arachnoid forms the morphological basis of the blood–brain barrier, which also explains Goldmann’s finding that the CSF remained colorless after intravenous trypan blue dye injection. Under normal physiological conditions, the barrier formed by the arachnoid remains intact following intravenous administration of Gd-DPTA and prevents leptomeningeal contrast enhancement, as found for example in meningeval carcinomatosis. In the current study, except in three cases in which we found borderline edema, migration of contrast agent into peritumoral tissue was always evident on the postinjection images. Spreading of contrast medium from an extraaxial meningioma into brain tissue represents an obligatory loss of the physiological barrier function and an increased permeability of the arachnoid. The high level of concordance between contrast agent spreading and the incidence of peritumoral brain edema in 91% of cases underscores that the loss of the barrier function of the leptomeninges represents one of the key steps or perhaps the essential step in the generation of edema in meningiomas. In the meningiomas without edema, evidence of contrast agent crossing into brain parenchyma was consistently absent, indicating that the leptomeningeal barrier function remained intact.

Some meningiomas without surrounding edema showed contrast enhancement of the peritumoral subarachnoid space on the postinjection images, although contrast agent spreading into the brain tissue was lacking. Increased permeability of the arachnoid must have existed in these cases as well. Apparently, the clearance function of the adjacent subarachnoid space remained adequate to prevent the extravasation of contrast agent and the development of edema. In addition to playing an important role in the resorption of edema, the clearance function of the ventricular system may also defend the brain against the spreading of substances capable of causing edema even when the arachnoid has already become permeable in cases without significant obliteration or adherence of the subarachnoid space. Thus, an intact subarachnoid space likely exerts an important influence on the elimination of substances able to induce edema elucidated by tumor.

Consistent with the present findings, information from intraoperative angiography, and histological studies provides evidence that the key pathogenetic alteration in the development of edema occurs within the leptomeninges, specifically the arachnoid.

Salpietro and colleagues conducted an intraoperative study to ascertain whether edema occurs within the arachnoid. Meningiomas with smooth brain–tumor interfaces demonstrated intact subarachnoid spaces, appearing to correlate with an absence of peritumoral edema. In the transitional tumor type, the highly thinned arachnoid adhered closely to tumor with interruptions in the arachnoid found in 14.3%. Moreover, communicating cerebral arter-
ies between brain and tumor were frequently found. This tumor type tended to show halolike peritumoral edema with varying volumes. In contrast, the invasive tumor type often adhered very closely to the pia mater. Typically, infiltration into the cerebral cortex could be demonstrated, showing direct contact between tumor and white matter. This type was frequently associated with massive edema.

Furthermore, a close correlation between the pial blood supply from cerebral arteries to meningiomas and the presence of edema was determined.4,16 A communication between the blood supply to meningiomas from the cerebral circulation belies the close morphological relationship between the tumor surface and the adjacent brain tissue. Contrary to physiological conditions, the arachnoid is no longer a barrier to cerebral arteries in cases of a pial blood supply to an extraxial tumor, indicative of disintegration of the arachnoid.

Histological analysis also showed that the most consequential pathogenetic changes leading to the development of edema occur at the brain–tumor interface.5

Contrast Agent Spread in Brain as Evidence of Pressure Gradients Within Edema

Because contrast enhancement within the tumor on T1pi images was virtually identical between meningiomas with and without edema, it can be assumed that the contrast agent concentrations in the extracellular space were essentially the same in both groups of tumors. A process based solely on unimpeded diffusion would be expected to show fairly similar speeds of contrast agent movement based on the unchanged diffusion constant for Gd-DPTA.

On the contrary, these results demonstrated that in meningiomas with edema, the distance traversed by the contrast agent front, as seen in the T1pi and T1pi series, depended on the volume of edema. The speed of marker spreading within brain edema correlated with the size of the edema, a relation that refutes the pure diffusion hypothesis. Instead, the dependence on edema volume indicates that similar conditions exist in peritumoral edema associated with meningiomas, as in experimentally induced vasogenic edema in the cold-injury model.

Reulen, et al.,25 used this model to show that extracellular markers with completely different diffusion coefficients had identical speeds of spreading in otherwise identical experimental conditions. These authors ascribed the primary mechanism of marker movement to bulk flow caused by interstitial pressure gradients. In fact, the interstitial pressure gradient with the highest values was measured within the vasogenic edema at the location of peripheral damage with decreasing values observed toward the ventricular system.25,26

In contrast to that model, a single marker with a constant diffusion coefficient was used in our study. Furthermore, the edema volumes in our study were highly variable rather than similar in size. Because the interstitial pressure in vasogenic edema depends on the amount of water present,25 a relationship between the size of edema and interstitial pressure gradient can be assumed.

Thus, the variability in interstitial pressure gradients occurring with different edema volumes can explain the various speeds of contrast agent progression measured in the current study.

The interstitial osmotic pressure is generally higher in tumors than in normal tissue.18,31 If this increased interstitial pressure in meningiomas is transferred to brain parenchyma in the absence of the leptomeningeal barrier function, then the development of pressure gradients in brain tissue must result as an unavoidable consequence.

Thus, contrast agent spreading in the brain represents a process initiated by bulk flow, which in turn is based on interstitial pressure gradients.

The contrast agent spreading from tumor into brain tissue caused by pressure gradients observed here depends on preexisting alterations in the peritumoral subarachnoid space. A completely intact subarachnoid space between tumor and brain that communicates freely with the rest of the CSF prevents the development of pressure gradients between the extracellular space of the tumor and the intraventricular space of the brain, because a constant pressure exchange would occur. In addition to the increased permeability of the arachnoid, adherence between the arachnoid and the pia mater is a required pathogenic precondition for the generation of pressure gradients, which cause either a direct communication between the tumor and the brain or trapping of CSF fluid within enclosed areas of subarachnoid space. The aforementioned intraoperative and MR imaging observations and the histological alterations at the tumor–brain interface confirm the validity of the hypothetical considerations.2

Role of the Secretory–Excretory Phenomenon in Development of Edema

Philippon and colleagues22 first proposed the pathomechanism of a secretory–excretory phenomenon for the development of edema in meningiomas. Based on electron microscopic evidence, they noted signs of secretory–excretory activity in tumor cells which correlated closely with the production of perifocal edema. The existence of the rare subgroup of WHO Grade I tumors, the secretory meningiomas, supports this hypothesis. Algucuicil-García and colleagues1 suggested the designation “secretory meningioma” based on immunohistochemical and electron microscopic characteristics of increased secretory activity. This histological type, accounting for approximately 3% of all meningiomas,23 is remarkable because of the unusual epithelial differentiation of the meningothelial cells. The cellular inclusions are periodic acid–Schiff positive, with immunohistochemical evidence of carcinoembryonic antigen, epithelial membrane antigen, cholecystokinin, α1-antitrypsin, α1-antichymotrypsin, and immunoglobulins. The incidence of edema surrounding secretory meningiomas is estimated at approximately 80%; however, even more striking than the high incidence of edema is the propensity of secretory meningiomas to produce particularly voluminous edema. Probst-Cousin and colleagues23 examined 31 secretory meningiomas in which edema encompassed the patient’s entire hemisphere in 64% of these cases. Frequently even small tumors generate large edema volumes. Likewise in the present study, the tumor showing the greatest edema index was a secretory meningioma.

Secretory meningiomas also occur without edema; however, when edema is present, the extent is massive. Probably the crossing of edema-producing substances is
Hydrodynamics in pathogenesis of edema surrounding brain meningiomas

also prevented in secretory meningiomas as long as a functional barrier between brain and tumor exists. When the leptomeningeal barrier deteriorates, substances secreted by the tumor are released that can then spread according to hydrodynamic principles into the adjacent brain parenchyma. Substances actively secreted from secretory meningiomas exert greater edema-producing effects than passively filtered plasma components from other types of meningiomas. This supposition is substantiated by our observations of a secretory meningioma, in which the amount of contrast agent extravasated into the brain tissue according to hydrodynamic processes was disproportionately small compared with the edema volume present. This serves as evidence that the substances elicited from this tumor type more effectively induce edema than those found in other tumors.

In the most recent literature, the significance of VEGF in the neovascularization of tumors and the development of edema has garnered increased interest. The secretion of VEGF could also play a role in the generation of edema associated with meningiomas. The incidence of VEGF expression appears to be significantly increased in meningiomas with edema. It is conceivable that VEGF crosses into the peritumoral brain parenchyma and produces edema in cases in which the leptomeningeal barrier has deteriorated.

Hydrodynamic and secretory processes could possibly represent synergistic mechanisms in the development of edema. In both cases, disruption of the leptomeninges and generation of pressure gradients are necessary prerequisites. Additionally, the fluid extravasated by the tumor shows an actively altered composition in cases with secretory components.

Our observations suggest that the key pathogenetic hydrodynamic processes can be influenced by the administration of corticosteroid agents. In addition to changing the permeability of tumor vasculature, permeability of altered arachnoid membranes may be influenced as well, explaining the reduction in contrast agent spreading from tumors in patients receiving corticosteroids.

Conclusions

Our results show that significant contrast agent effusion from the extracellular space of the tumor into the interstitium of the peritumoral brain tissue is only found in meningiomas associated with edema. This supports the hypothesis that hydrodynamic processes, probably based on arachnoid disintegration and adhesions in the subarachnoid space, play an essential role in the pathogenesis of peritumoral brain edema in meningiomas.

References


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