

Peritumoral brain edema in relation to tumor size is a variable that influences the risk of recurrence in intracranial meningiomas

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Abstract

Background

Peritumoral brain edema (PBE) is common in intracranial meningiomas (IM) and can increase its morbidity. It is not uncommon for a neurosurgeon to face the diagnosis of a meningioma with a large proportion of PBE irrespective of the site and size of the contrast-enhancing lesion without any clinical and biological cause.

Methods

We performed a retrospective review of 216 surgically-treated patients with IM. We recorded clinical, biological, and radiological data. Based on the rate of tumor and edema volume, we divided the patients into a group with high-ratio Edema/Tumor and a group with a low ratio. We investigated how the ratio of edema/lesion may affect the outcome.

Results

Multivariate analysis was performed for the two groups. Smokers were more frequently associated with the high-rate group. The edema/tumor ratio does not influence surgical radicality, however, independently of the biological subtype, WHO grading, and EOR, a higher frequency of recurrence is shown in patients with a high edema/tumor ratio (70.5% versus 8.4%. $p < 0.01$).

Conclusions

The relationship between tumor and edema volume is respected in our series, but it does not explain why there are so many cases in which the ratio is so high. It seems that the blood-brain barrier (BBB) damage from smoke could have a role in an increased volume of PBE.

Introduction

Meningiomas are benign neoplasm arising from meningoendothelial cells [1]. They are the most frequent intracranial tumor in the adult population. Although intracranial meningiomas (IM) are typical extra-axial tumors, the occurrence of peri-tumoral brain edema (PBE) is not rare, affecting between 38 and 67% of patients affected [1–3]. It is well recognized that a large proportion of PBE can increase morbidity and mortality [2] determining brain displacement, increasing intracranial pressure[3], and the risk of perioperative epilepsy [4]. In daily clinical practice, it is not uncommon for a neurosurgeon to face the diagnosis of an IM with a large proportion of edema irrespective of the site and size of the contrast-enhancing lesion (**Fig. 1**).

Despite the relatively large number of studies on this topic [1, 5–7], the mechanisms by which an IM produces PBE are not fully clarified. Furthermore, none of the published hypotheses on molecular mechanisms can explain the genesis of PBE and its role in clinical outcomes [3]. In this retrospective study, we investigated several possible clinical and biological variables that may result in a higher proportion of edema at IM diagnosis. We subsequently investigated how a high ratio of edema/lesion may affect clinical and surgical outcomes.

Methods

We performed an Institutional retrospective review of the imaging of a consecutive series of surgically-treated patients suffering from World Health Organization (WHO) 2021 histologically confirmed IM, operated on in Sapienza Neurosurgery Department of Rome (Italy) and Neurosurgery department of Hospital Spaziani of Frosinone (Italy) in the period ranging between January 2016 and December 2020. We collected a total of 216 patients suffering from IM.

For all the included patients, we recorded sex, age, time of follow-up, length of hospitalization, clinical onset, smoke habit, comorbidity, and performance status (measured using the Karnofsky performance scale (KPS) at the moment of radiological diagnosis. Regarding the clinical onset, we considered focal neurological deficits the focal disorders of body motility and sensitivity, sphincter disorders, and disorders involving cranial nerves, including visual disturbances. We also considered the presence of dizziness, alteration of mental status and memory loss, the presence of intractable headache, seizure, and the incidental diagnosis.

On the ground of the final histological diagnoses, we recorded: WHO grading with subtypes, Immunohistochemistry with Ki67, and Progesteron Receptor (PR) expression. Concerning the radiological evaluation, we recorded parameters such as the location of the lesion, the involvement of the subtentorial compartment, tumor major diameter (measured in cm), and tumor volumes (measured in cm^3) using isotropic volumetric T1-weighted sequences before and after intravenous administration of paramagnetic contrast agent (gadolinium); We used T2-weighted and Fluid Attenuated Inversion Recovery (FLAIR) sequences to obtain the edema volumes (measured in cm^3 before anti-edemigen therapy). Volume of the contrast-enhancing lesion and edema was calculated drawing a region of interest (ROI) in a Volumetric enhancing post-contrast study weighted in T1 (a multi-voxel study) and T2, conforming to the margins of the contrast-enhancing lesion with software Horos [8] following our institutional previous published protocol for IM [9].

From these parameters we calculated the rate between tumor volume and edema volume, obtaining a binomial variable that divides into two groups:

Group A, High-ratio Edema/Tumor

the volume of edema is equal to or greater than that of the contrast-enhancing lesion (with a numerical rate < 1);

Group B, Low-ratio Edema/Tumor

the volume of edema is lesser than that of the contrast-enhancing lesion (with a numerical rate > 1) or lesions without quantifiable edema;

Overall survival (OS) was recorded in months, and it was measured from date of diagnosis to date of death or date of the last contact if alive. Clinical information was obtained by our Institution's digital database, whereas OS data were obtained by telephone interview. We recorded after the surgical procedure the status of performance (using KPS) for each patient at one month, six month and at the last clinical evaluation. A particular focus was on the KPS results: such parameter was considered, as previously observed, predictive and associated with survival (methodology described for other studies reported). We evaluated the presence of complications, recurrence, and consequent second treatment by recording biological switch. We investigated whether the large diameter on radiological diagnosis indicates different OS, grading, immunohistochemical characteristics, and clinical/neurological outcome.

Statistical methods

The sample was analyzed with SPSS version 18. We examined the relationship between these factors and brain edema through univariate and multivariate analyses.

Comparisons between nominal variables has been made with the Chi² test. The extent of resection (EOR, measured with Simpson Grade) means was compared with One Way and Multivariate ANOVA analysis and Contrast analysis and Post-Hoc Tests. Continuous variables correlations have been investigated with Pearson's Bivariate correlation. The threshold of statistical significance was considered $p < .05$.

Data reported in the study have been completely anonymized. No treatment randomization has been performed for its retrospective nature. This study is consistent with the Helsinki Declaration of Ethical principles for medical research for humans.

Results

At first radiological analysis, we confirm the presence of a positive correlation between the increasing contrast-enhancing lesion volume and the edema volume measured in T2-FLAIR by Pearson's bivariate correlation analysis ($p < 0.01$). The appropriateness of the division in two groups is confirmed by the fact that while there is a significant difference between the average volumes of edema between group A and group B ($p < 0.01$), this difference is lost when comparing the average volumes of contrast-enhancing lesions ($p = 0.99$).

From a clinical perspective, the comparison between the two subgroups showed no significant differences in variables such as age ($p = 0.15$), sex ($p = 1$), and comorbidity ($p = 0.32$). On the other hand, smokers were more frequently associated with the group with a high rate of edema/tumor ($p = 0.02$, Fig. 2 part A). Clinical onset in subjects with a high edema/tumor ratio is more frequently associated with the

presence of seizures ($p = 0.05$) and with a non-significant difference in performance (measured by KPS) at onset (mean 70 versus 80, $p = 0.18$).

Localization does not affect the edema/tumor ratio (ANOVA $p = 0.34$), although a weak correlation is evident with convexity meningiomas compared to deep or subtentorial meningiomas ($p = 0.06$). On the other hand, if we consider only frontal meningiomas, there is a high percentage of highly edemigenous meningiomas with a high edema/volume ratio ($p = 0.03$, Fig. 2 part B).

Biological variables such as Ki67%, biological subtype, and progesterone expression do not significantly correlate with the total edema volume or the value of the edema to lesion ratio. It is confirmed that the grading of meningiomas is an independent variable about outcome, but that it has no direct correlation with edema volume.

In the outcome measures, we compared the two groups with multivariate analysis considering WHO type, biological type, location, and EOR. We do not note a higher rate of complications (including ischemia $p = 0.39$ and infection $p = 1$), postoperative seizures ($p = 0.49$), mortality, and hospitalization time ($p = 0.51$) between the two groups ($p = 1$). Surgical radicality, as measured by Simpson's grade, is not influenced by the edema/tumor ratio with non-significant differences ($p = 0.42$); however, independently from the biological subtype, WHO grading, and EOR, a higher frequency of recurrence is shown in patients with high edema/tumor ratio (70.5% versus 8.4%. $p < 0.01$).

We obtained similar data by measuring with t-student tests the relationship between edema volume and risk of recurrence: IMs which presented greater tumor edema at the diagnosis were more likely to recur if compared to those which never recurred (42.3 cm³ versus 26.62 cm³, $p = 0.04$, **Fig. 3**).

Discussion

PBE is found in approximately 50% of meningiomas [1], and it may be present in variable degrees and in an unpredictable fashion [9]. The relationship between the volume of edema and the tumor often appears to be coincidental at the time of diagnosis. This latter may result from a conjunction of the different mechanisms. Although meningiomas are benign tumors, they are often accompanied by brain edema that causes clinical symptoms [6,7,10]. Clinically, peri-operative morbidity and mortality in meningioma surgery may be attributed to PBE [11]. Hence, significant brain edema may cause severe neurologic deficits and limit the surgical field during the approach [12].

In this study, we hypothesize that it is not so much the absolute value of the volume of PBE found worthy of investigation but the relationship between the size of the tumor and the volume of edema it generates. The relationship between tumor volume and edema volume is also respected in our series. Still, it does not explain why there are so many cases in which the edema/tumor ratio is so high. We identify a subgroup of IM with a very high capacity to generate PBE concerning its volume. We found that IM patients with high edema more frequently debut with seizures. Among all the risk factors investigated

and known, the only one that seems to have an association with a high edema/lesion ratio is the smoking habit.

The possible role of smoking in the development of meningioma is still unclear, but although the nicotine itself does not affect the blood-brain barrier (BBB), it seems there is an increase of the permeability with loss of function in vivo in the smokers of this compartment [13]. PBE originates in the margin regions of the tumor, suggesting a vasogenic origin and a pathogenic mechanism that primarily links IMs with BBB disorders.

Biologically, no data correlates with an onset of IM with a high proportion of edema. Although previous studies reported that angiomatous and meningothelial types tend to be associated with more significant brain edema [14], such a clear association trend was not identified in our study.

We confirmed that WHO high-grade meningiomas independently correlate with a worse outcome [15] and an elevated risk of recurrence in patients. However, the most interesting finding of our study demonstrates that although there is no direct relationship between tumor grading and the amount of edema, more edematous meningiomas have a higher risk of recurrence over time independently of the Simpson grade achieved with surgery.

We hypothesize that an increased permeability of the BBB assisted by an increased vascular supply in the surgical cavity [16,17] during the post-surgical phase may increase the risk of recurrence or regrowth in predisposed subjects. The presence of edema suggests just the greater predisposition to recur, independently of the patient's grading, ki-67 expression, and hormonal receptor status.

The two groups examined do not present, once surgically treated, significant differences in clinical outcomes, EOR, and postoperative complications. The status measured with the KPS does not show differences between the highly edematous tumors at the onset compared to the others. However, we suggest for this particular subgroup of patients a more careful and restricted clinical and radiological follow-up.

In our results and experience, the cause of PBE associated with meningioma is most likely multifactorial. The location of the dural attachment can be considered a factor predisposing to the development of more significant edema. This is also demonstrated in our study where anterior cranial fossa meningiomas compared to other locations and convexity meningiomas compared to deep meningiomas are associated with more significant peritumoral edema.

However, this finding must be, in our opinion, considered with caution; anterior convexity meningiomas are the most common and the ones most likely to reach large sizes before becoming symptomatic, so there may be selection bias.

Another possible explanation that may account for such a large subset of meningiomas being edemigenous independently of tumor volume and biological status lies in the differences in vascularity among IMs. Smith et al. [18] found that tumors with increased cellularity, vascularity, and mitotic activity had edema more frequently. Challa et al. [19] reported that more vascular tumors tend to have a breakdown of capillary endothelial tight junctions, leading to increased permeability to water. Also, high vascularity may cause increased water content in the tumor. However, at the moment, there are no objective methods capable of quantifying the vascularity of a meningioma, and therefore this data can only be considered a hypothesis.

Further study and limitations

A potential source of bias is expected to derive from the exiguity of the sample, which nevertheless, in regards to the endpoints selected, presents an excellent post-hoc statistical estimated power (difference between two independent means; $1 - \beta = 0.9488$ for $\alpha 0.05$ and effect size 0.5), thus providing highly reliable conclusions.

Conclusion

Many investigations have been carried out to determine the pathogenesis of PBE, but the exact pathogenesis in meningiomas is still unknown, although most likely multifactorial.

This study demonstrates that meningiomas that show a high ratio of PBE to tumor volume at diagnosis are more frequent in smokers and correlate with a higher incidence of recurrence independent of biological type and grading.

Declarations

Funding: This study was no funded by any association.

Conflict of Interest: We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work.

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Availability of data and material: The study does not have repository data. Data are available in an institutional database that can be purchased from the corresponding author (DA).

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Code availability: not applicable

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors.

Informed consent to participate: Informed consent was obtained from all individual participants included in the study. The patient has consented to the submission of this review article to the journal.

-

Consent for publication:

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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Abbreviations

Peri-tumoral brain edema (PBE), intracranial meningioma (IM), World Health Organization (WHO), Karnofsky performance scale (KPS), Progesteron Receptor (PR), Fluid Attenuated Inversion Recovery (FLAIR), region of interest (ROI), Overall survival (OS), Extent of resection (EOR), blood-brain barrier (BBB)

Tables

Table 1: Patients demographics

216 patients	Group A High Rate (61 pts)	Group B Low-rate (155 pts)	P-value
Female sex	41	113	0.41
Age (mean)	60 ± 14.91	59.7 ± 13.6	1
Follow-up (months)	45.93	46.2	1
Hospitalization (days)	17.77	19.82	0.77
Smoke	26	43	0.02
Comorbidity	18	50	0.32
High grade WHO	12	25	0.55
Convexity Location	26	66	0.06
Subtentorial	1	17	0.27
Supratentorial	60	127	0.27
Frontal Location	34	61	0.07
Diameter (mean cm)	4.6	4.48	1
Tumor volume (mean cm ³)	35.42	37.87	0.99
Edema Volume (mean cm ³)	80.68	7.72	<0.01
ki67%	8%	5%	0.26
PR+	8	20	0.55
Clinical debut	Incidental Dizziness Focal deficit Headache Seizure Mental alteration	Incidental Dizziness Focal deficit Headache Seizure Mental alteration	1
Seizure at debut	19	30	0.05
KPS at onset (mean)	70	80	
Post-operative KPS	70	70	
KPS at last evaluation	80	90	
Seizure after treatment	9	20	0.49
Complications	14	37	0.51
Recurrence (no. patients)	43 - 70,5%	13 - 8,4%	0.01

Figures

Figure 1

In the figure, we compare two cases of patients with frontal lobe meningioma with an asymptomatic onset that on MRI images document entirely different volumes of edema. In the first case, T1-weighted with MDC (A), T2-weighted (B), and FLAIR (C) images show a 2 cm para alpine lesion with edema involving the entire frontal lobe. In the second case, the identical sequences (D, E,F) show a more than 4.5 cm lesion in diameter with a volume of edema almost absent.

Figure 2

Chi-square Comparison Analysis shows statistically significant differences in the smoking habit in subjects with a high edema-to-tumor volume ratio (Fig. 2A, $p=0.03$). The latter have a significantly increased risk of developing recurrence independently compared with meningiomas with a low ratio (Fig. 2B, $p=0.02$).

Figure 3

In the box letter graph, there is a significant difference between the group of patients developing recurrence with the total volume of edema ($p=0.04$). This difference appears to be independent of WHO grade.