Chemical Aspects of Peritumoral Cerebral Edema in Atypical Meningiomas

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Aim of this study was to perform a retrospective evaluation of the radiological, clinical and pathological features influencing the occurrence of peritumoral brain edema (PBE) and understanding the responsible chemical mediators involved. We have examined magnetic resonance imaging(MRI), symptoms and pathology for 25 patients with convexity atypical meningiomas (WHO grade II), who underwent surgery at Professor Dr. N. Oblu Emergency Clinical Hospital between 2010 and 2017. We evaluated the possible prognostic factors related to peritumoral edema including: demography (age, gender), pathology (anatomical localization of the tumor, tumor volume, brain invasion, shape of tumor margin), symptoms and neuroimaging characteristics such as high signal intensity of the tumor on T2-weighted images (T2WI), contrast enhancement and heterogeneity. Age, gender, anatomical location of the tumor and brain invasion were not correlated with peritumoral edema. Also, the neuroimaging characteristics (homogeneity, high signal intensity on T2WI, high contrast enhancement) or the presence of motor deficit were not statistically significant regarding the relationship with the edema. Peritumoral edema and irregular tumor margins were statistically significantly (p=0.03). Tumor volume was not associated with the peritumoral edema. We also found other significant statistical correlations of the radiological features, which are worth mentioning: high-contrast enhancement with the age of the patient (p=0.006), high signal intensity on T2WI with tumor volume (p=0.03) and tumor heterogeneity with irregular tumor margins (p=0.002). The results of this study demonstrate that an irregular tumor margin may be an important predictive factor that would influence the occurrence of peritumoral edema in atypical meningiomas.

Keywords: peritumoral brain edema, atypical meningiomas, convexity meningiomas, MRI characteristics, cerebrospinal fluid

Meningioma is an intracranial tumor of extracerebral origin that possesses the ability to produce PBE in least half of the cases of meningiomas in varying degrees and in an unpredictable manner [1, 2].

Of all meningiomas, atypical meningiomas (AMs) represents an intermediate risk group between benign (grade I) and anaplastic/malignant (grade III) meningiomas [3], with an incidence that has increased in recent years [4, 5]. In our country, this increase was also attributed to the exposure of ionizing radiation after Chernobyl accident, which also produces brain damage *in utero* [5].

Although several factors have been correlated with PBE such as tumor size [6-12], tumor location [7, 8, 11-13], tumor histology [12], vascularization [12], VEGF production [6, 14], prostaglandins [15], interleukin-6 expression [16] or the hydrodynamic factors that break the blood-brain barrier [8, 17], the mechanism of the occurrence of edema in meningiomas has not been fully elucidated.

The present study aims to determine which demographic, clinic, pathogenic and neuroimagistic characteristics are correlated with peritumoral edema in atypical meningioma (AM).

Experimental part

Materials and methods

We carried out the retrospective follow-up of 25 patients with AMs of convexity (WHO grade II) histologically confirmed and operated in Professor Dr. N. Oblu Emergency Clinical Hospital Iasi during 2010-2017. A head-MRI was performed to all patients prior to surgery and we examined the correlations between PBE and age and gender (demographics), anatomical localization of the tumor, tumor volume, brain invasion, shape of the tumor margin (pathological characteristics) and symptoms, as well as the high signal intensity of the tumor on T2WI, contrast enhancement and heterogeneity (neuroimaging characteristics).

From the MRI neuroimaging there was measured the approximate tumor volume, by using the formula for a spheroid: volume = $4/3\pi$ x abc (fig. 1). That is how we calculated the volume of the elliptical sphere, with the help of the maximal perpendicular diameters of the tumor from the axial image (radii a and b) and diameter of the tumor from the coronal image (radius c).

The presence of brain edema was evaluated as a high-intensity extension adjacent to tumor on T2WI. PBE was graded by using the following scale: (0) no edema:

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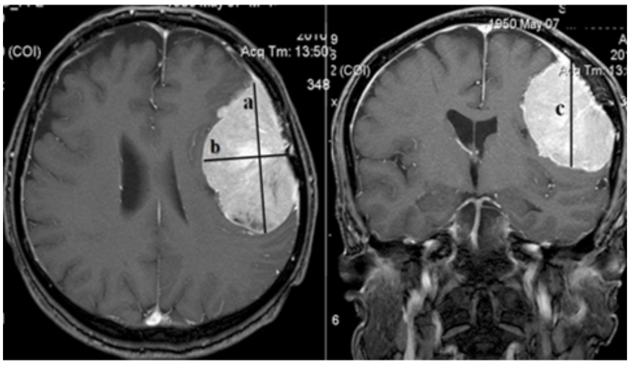

Fig.1. The size of the tumor was measured (a, b and c) and the resulting volume was then approximated using the formula for elliptical sphere: volume = $4/3\pi$ x abc

absence of increased T2WI surrounding the meningioma, (1) mild edema: crescent or rim of increased T2WI surrounding the meningioma without mass effect, (2) moderate edema: more extensive than an increased T2WI surrounding the meningioma without mass effect and (3) severe edema: mass effect from PBE with/without deep edema fingers [9] (fig. 2 A-D). The signal intensity on the T2WI was classified as high signal intensity and low/iso signal intensity. Tumor margins were classified as smooth or irregular. The statistical analysis was carried out with SPSS 13 for Windows.

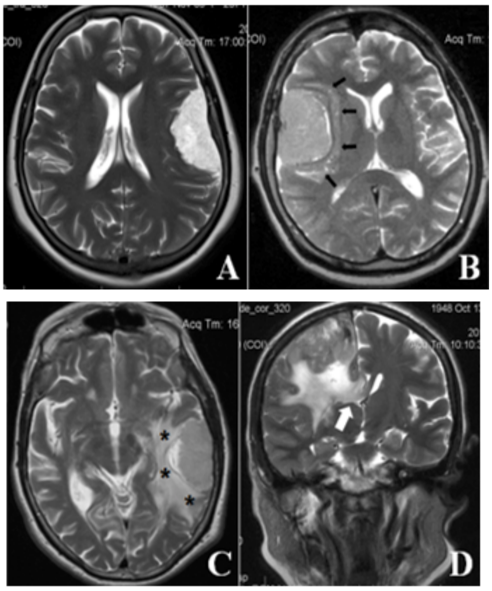

Fig.2. Edema scale: 0 - no edema (A), 1- mild edema, with crescent or rim of increased T2WI surrounding the meningioma (black arrows) (B), 2 - moderate edema with more extensive increased T2WI without mass effect (black asterisk) (C), 3 - severe edema with mass effect and compression the lateral ventricle (white arrow) (D)

Results and discussions

PBE is found in more than half of meningioma cases [7, 18], and its preoperative recognition is important, because it has been associated with poorer clinical outcomes in patients [19-26]. This is due to the fact that PBE creates technical difficulties when accessing the tumor by limiting the surgical field [23, 20]. It may also cause new neurological deficits [23, 27], aggravate preexisting ones and increase the risk of intracranial hematoma [28] or intracranial hypertension in the postoperative period [23]. In this regard, medicine faces various legal and ethical issues, in which the decision to carry out the treatment is taken together by patient and surgeon for the benefit of the patient and respecting his personal values [29, 30].

There have been proposed mechanisms for edema failure of the blood-brain barrier [31] or for the increased permeability through white matter fibers that become relatively loose around the tumor [7, 32, 33]. However, the causes of PBE have not been identified and the exact pathogenesis of edema has not been explained yet.

Mechanisms of cerebral edema. Klatzo was among the first to describe vasogenic edema as the increase of the capillary permeability that leads to protein and fluid extravasations into the interstitial space, in special into white matter [10, 34]. Also, edema fluid composition in experimental models is similar to plasma, hence the idea that the fluid is of intravascular origin [10] (table 1). In addition to vasogenic edema, studies show that, in the case of some patients with meningiomas, edema also has an ischemic component due to compression of the adjacent brain parenchyma by the tumor [35]. This happens especially in the case of large meningiomas that compress the adjacent brain and may tear, therefore, the arachnoid membrane with the secondary increasing edema [20].

Table 1
CONCENTRATIONS OF INTERSTITIAL FLUID, PLASMA AND CEREBROSPINAL (CS) FLUID [60, 61]

Species	Interstitial fluid	Plasma	CS fluid
Na^+	146 mM	142 mM	154 mM
K^+	4.1 mM	5.0 mM	3.0 mM
Cl^-	118 mM	103 mM	128 mM
HCO_3^-	22 mM	27 mM	23 mM
pH	7.2-7.4	7.35-7.45	7.2-7.4

Vasogenic edema is also associated with increased vascular permeability. Studies demonstrate correlations between PBE, overexpression and tumoral secretion of vascular endothelial growth factor (VEGF) [6, 36-40], aquaporin 4 [41-44], the expression of matrix metalloproteinase-9 (MMF-9) [37, 45, 46], E-cadherin and beta-catenin [47] or interleukin-6 [16]. Understanding these mechanisms could lead, in the future, to the development of various therapies for adjuvant treatments [48] and antiproliferative activity agents against meningioma [49, 50], such as flavonols and flavones from wine [51].

AMs, as well as malignant meningiomas have been correlated with extensive PBE, on the one hand, due to increased cellularity, vascularity and mitotic activity [52], but also due to the effects on the physiological barrier in the tumor-brain interface [2]. In our 25 AMs series, we noticed that more than half of the cases (60%) were accompanied by peritumoral edema in an F: B ratio of 1:1.1, in agreement with previous studies claiming that PBE is frequently met in AM [32, 53]. In relation to edema classification (fig. 2 A-D), out of the 15 AMs with PBE, most had severe form (8 patients), followed by moderate edema (3 patients) and mild edema (4 patients).

Regarding the localization of meningiomas at convexity level, they are more prone to peritumoral edema, unlike meningiomas arising from the parasellar or orbito-frontal base regions with neuro-ophtalmological involvement, middle or posterior fossa [2, 8, 13, 54]. These differences have been explained by some authors through the existence of multiple arachnoid layers in the sellar region [55] and through the fact that the meningiomas of the posterior fossa are usually observed at an early stage and that there is less white matter in the posterior fossa than in the supratentorial space [54].

Age, gender and edema. In terms of demography, out of the 25 patients, 12 were men and 13 women, ranging in age from 42 to 86 years (mean age 63.32 years). In both men and women, more than half of them had PBE (table 2). Pre-existing studies report that gender and age were not correlated with PBE [8, 20, 23, 26, 54, 56]. We reached the same conclusion, although some studies suggest that the male gender is significantly correlated with PBE [2]. No statistical correlation was observed between edema and age or gender. Instead, we found that the relationship between age and high contrast enhancement was significant (*p=0.006*), whereas AM intensely enhanced contrast substance in the case of elderly people (> 60 years). We also found a significant correlation between gender and tumor volume, in the sense that men are prone to develop larger AM than women (p=0.02).

Table 2
DISTRIBUTION BY GENDER OF PERITUMORAL BRAIN EDEMA

Gender	Edema	No edema	Total
Female	7 (53.84%)	6 (46.150%)	13 (100%)
Male	8 (66.66%)	4 (33.33%)	12 (100%)
Total	15 (60%)	10 (40%)	25 (100%)

Anatomical localization, brain invasion and edema. Regarding the localization of tumors, 40% were frontal (10 patients), while the remaining 60% were distributed as follows: frontoparietal (5 patients), frontotemporoparietal (2 patients), temporal (2 patients), parietal (2 patients) and occipital (2 patients). Our study did not find any statistical significance between anatomical localization and PBE, just as other authors [2, 56, 57]. In terms of invasion of the brain, out of a total of 25 meningiomas, we found brain invasion in 6 patients (24%), but without statistical correlation with PBE or other features followed by us.

Clinical findings and edema. Regarding the symptoms of patients, we found no correlation between motor deficit, intracranial hypertension syndrome and PBE, which is in agreement with the results of other studies [20].

Tumor volume and edema. The average volume of AMs was 43.68 cm^3, ranging from 5.65 cm^3 to a maximum of 226.42 cm^3. We found no statistical significance between tumor volume and PBE, just as a certain number of papers that reported the same conclusion [12, 13, 32, 45, 56, 58].

Shape of tumor margin and edema. In MRI neuromaging, we also evaluated the margins of the tumors, considering them smooth (smooth edges, no irregularities or nodularity) and irregular type (anfractual margins, with nodularity). Out of a total of 25 AMs, most tumors had irregular edges (14 cases), compared to 11 cases with smooth edges. We also found a statistical correlation between irregular margins and edema: the AM of the irregular type is more likely to be accompanied by PBE (p=0.03), in agreement with some studies [8, 20, 32, 57]. Some authors agreed that one of the most important factors in the formation of peritumoral edema is the tumor-brain interface [1, 7, 8, 20, 59] and Simis *et al.*(2008) reinforced the hypothesis that an irregular interface brain - tumor favors brain invasion and the occurrence of edema [20] (table 3).

Intensity of the tumor on T2WI and edema. A high signal on the T2WI of the tumor indicates a high water content and increased vascularity, which makes the high water content easily spread to neighboring areas due to differences in osmotic pressure [2, 8, 57]. We have not identified a significant correlation between it and brain edema. It seems that in our series of cases, high signal intensity on T2WI does not accompany PBE, although preexisting studies have shown that high signal meningiomas on T2WI causes important swelling [32]. Instead, we found a strength correlation between tumor volume and T2WI signal (p=0.03). We also found a significant correlation between AM homogeneity and its margins: the more non-homogenous the tumor is in neuroimaging, the more irregular its margins are (p=0.002).

Table 3
RELATIONSHIP BETWEEN TUMOR MARGINS AND PERITUMORAL BRAIN EDEMA

Tumor margin	Edema	No edema	Total
Smooth	4 (36.36%)	7 (63.63%)	11 (100%)
Irregular	11 (78.57)	3 (21.42)	14 (100%)
Total	15 (60%)	10 (40%)	25 (100%)

Conclusions

We consider that irregular tumor margins may be an important predictive factor for the occurrence of PBE in AMs. In the same manner, edema was not correlated with tumor volume or high signal intensity on T2WI. Thus, the results of this study demonstrate that irregular tumor margins can be an indicative parameter, which can predict brain edema that influences the clinical course of patients.

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