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MRI EVALUATION OF PERITUMORAL BRAIN EDEMA IN MENINGIOMAS- CORRELATION WITH AQUAPORINS 1,4 AND 9

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ABSTRACT **Aim:** To correlate presence of Peritumoral Brain Edema in cases of meningiomas with aquaporins 1, 4 and 9 in the tumoral brain tissue.

Settings and Design: Cross Sectional Descriptive Study

Material and Methods: The study included thirty cases of intracranial meningiomas that were managed at a tertiary care institute. Peritumoral Brain Edema was correlated with expression of Aquaporins 1,4 and 9 using immunochemistry.

Statistical analysis used: All calculations were done using the SPSS software version 14.0 for Windows.

Results: An approx 64.2 % cases with PTBE expressed AQP1 vis-a-vis only 6.2% cases without PTBE. An approx 85.7 % of cases with PTBE expressed AQP4 vis-a-vis only 6.2% cases without PTBE. AQP 9 expression was noticed in only 3 (10 %) cases out of total 30 cases. Although all these 3 cases had associated PTBE, rest of the 11 cases associated with PTBE did not exhibited expression of AQP9.

Conclusion: Expression of aquaporins 1 & 4 is associated with development of peritumoral brain edema in cases of meningiomas. No significant relationship was noted with the expression of aquaporin 9 and peritumoral brain edema. This finding may have an impact on the possible therapeutic target in improving the prognosis of intracranial meningiomas.

KEYWORDS : Intracranial Meningiomas, Peritumoral Brain Edema, Aquaporins 1,4 and 9.

INTRODUCTION

Intracranial meningiomas are the commonest extra axial tumors of the brain and they represent 15 % of all the brain tumors. Also, they are the commonest tumor of the meningeal origin.[1] The intracranial meningiomas are usually benign, known to be more common in female population and exhibit typical radiological and pathological features. However, they are well known to exhibit atypical imaging features occasionally and a small proportion of the intracranial meningiomas are also known to be high grade/malignant.[2]

Peritumoral brain edema (PTBE) is considered an important association of primary brain tumors. The literature has reported varying degrees of peritumoral edema in patients of intracranial meningiomas ranging from 38 to 67.2 %.The degree of edema may vary from barely noticeable to up to 2-3 times the volume of the tumor. PTBE if present, increases intracranial pressure and may induce neurological impairment. Also, PTBE makes surgical approach difficult and is known to influence surgical outcome, prognosis and recurrence.[3-5]

The precise mechanisms of the development of PTBE with meningioma have not been clearly defined. Various authors have studied correlation of PTBE with many factors, mainly the age of patient, location of tumor, tumor size, vascularity, signal intensity of tumor on T2WI and histology.[3,4]

Recent developments in the field of tumor biology of CNS neoplasms have unraveled various markers related to the development of PTBE and thereby contributing to the assessment of prognosis of these tumors. Of these, various kinds of aquaporins (AQP) have not only demonstrated a correlation with poor outcome in meningiomas, but have also shown possibility of being targets of newer therapeutic regimes.[6,7]

Peritumoral brain edema manifests on T2-weighted MR scans as high intensity areas surrounding the bulk tumor mass. The mechanisms of this increased fluid attraction and the cellular composition of the microenvironment are only partially understood.

Aquaporins(AQP) are a family of membrane protein water channels with an integral role in water transport and maintenance of fluid balance. These channels are widely distributed in all kingdoms of life, including bacteria, plants, and mammals. Aquaporins facilitate the transportation of water and in some cases, other small uncharged solutes, such as glycerol, CO2, ammonia and urea, across the membrane depending on the size of the pore. At least 11 AQP subtypes have been identified in mammals and the AQP family is subdivided according to their characteristics.[8]

Among AQP subtypes cloned in mammalian, only AQP1, AQP4, and AQP9 were identified in the brain. AQP1 is expressed in the epithelial cells of the choroid plexus, the cell producing cerebrospinal fluid (CSF). There have been studies quoting that AQP 1 participated in the biology and invasion of meningiomas.[9]

AQP4 is the predominant subtype present in the brain, with the most abundant site being in the perivascular glial process. AQP-4 expression was found to be increased in brain tumors compared to normal brain. Overexpression of AQP4 has been associated with significant PTBE.[8] Also AQP 4 expression has been found to be associated with PTBE in meningiomas.[7]

AQP9 is present in the cells surrounding the cerebral ventricles, including ependymal cells. The expression of AQP9 mRNA in astrocytic tumours was significantly greater than in normal brain tissue and was positively correlated with pathological grade which indicates that AQP9 may play an important role in the malignant progression of brain astrocytic tumors[10]. No study has been done relating expression of AQP 9 in cases of meningiomas.

This study endeavors to correlate the presence of aquaporins in tumor tissue with PTBE on MRI in cases of meningiomas which in turn may aid in opening new targeted therapy for brain edema.

MATERIAL AND METHODS:

This cross sectional descriptive study was carried out from September 2011 to August 2013 at Department of Radiodiagnosis and Imaging of a tertiary care and teaching hospital. The study was approved by institutional ethics committee.

Study Population:

The study included thirty cases of intracranial meningiomas that were managed at this tertiary care institute during study period.

Sample size:

A total of thirty patients were included in the final study. Sample size was reached based on the prevalence of cases in the institute, number of diagnosed cases finally going in for surgery and previous similar studies done by other authors.

Inclusion criteria:

All consecutive, non-repetitive patients radiologically diagnosed as cases of meningiomas were taken as the study group. Relevant clinical and imaging details viz. age, sex and details of contrast-enhancement on MRI were noted in respect of all the cases.

Exclusion criteria:

a) All known cases of recurrent meningiomas.

b) Unmatched radiological and histopathological tumour diagnosis. The cases which were diagnosed as meningiomas on imaging but turned out to be different tumor on histopathology were excluded.
c) Cases not willing to undergo surgery.
d) Associated history of trauma or stroke as they may independently cause PTBE.
e) Cases with additional pathology detected on MR or other imaging modalities.

Informed consent: was taken from all the patients as per WHO format.

Equipment used: All cases underwent MRI brain with 1.5 Tesla MRI scanner (Magnetom Symphony: Siemens; Germany).

IMAGING EVALUATION

All cases underwent MRI brain with 1.5 Tesla MRI scanner (Magnetom Symphony: Siemens; Germany).The conventional pre and post contrast sequences were included, namely axial T1, T2 weighted fast spin echo sequence, axial FLAIR, Difusion Weighted Imaging at b values, 0 ,500 and 1000 sec/mm2 and corresponding ADC maps and Gradient. Also, T1 sagittal and T2 coronal fast spin echo sequences were done.At the end of aforementioned sequences the patients were administered 0.2 ml/kg (0.1 mmol/kg) of IV Gadopentetate dimeglumine following which an axial T1WI and 3D Gradient sequences were performed. After obtaining the complete set of images, the following parameters were studied:

a) Size of the tumor. The maximum AP (diameter a) and transverse dimensions (diameter b) of tumor was calculated on the post contrast axial T1WI and the maximum longitudinal dimension (diameter c) of the tumor was calculated on the post contrast sagittal images. Following this the volume of the tumor was calculated using the formula for a spheroid i.e $4/3\ \pi$ axbxc in cubic centimetres.
b) Presence or absence of peritumoral brain edema (PTBE): This was studied on T2WI and FLAIR. The PTBE was identified by T2 and FLAIR white matter perilesional hyperintensity.
c) If a lesion showed presence of PTBE then the maximum anteroposterior, transverse and longitudinal dimensions were calculated for the tumor along with edema included. The volume of the tumor and edema combined was calculated using the same formula stated above.
d) After obtaining volume of tumor and volume of tumor + edema, edema index was calculated using the formula:Edema index= Volume (Edema+Tumour) / Volume (Tumour).

Histopathological Evaluation

The slides (H&E-stains along with relevant immunohistochemical stains) of all the cases were reviewed by a neuropathologist of 15 years experience, and the immunohistochemistry for Aquaporins 1,4 and 9 was done.

Statistical analysis

The results of the radiological data were evaluated along with histopathologic evaluation, those obtained on immunohistochemical studies for AQP-1, AQP-4 & AQP-9. The various variables that were included in the statistical analysis were:

a) Presence or absence of edema
b) Size/ volume of the tumor.
c) Edema index
d) Expression of AQP 1,4 & 9

All calculations were done using the SPSS software version 14.0 for Windows. P value < 0.05 was considered significant.

RESULTS

A total of thirty (30) patients of intracranial meningiomas were included in the study. The aim was to correlate peritumoral brain edema(PTBE) with aquaporins (AQP). P value <0.05 was taken as statistically significant. In the figures and diagrams following, PTBE has been characterized as "present" or "absent" whereas aquaporins as "positive" or "negative".

Tumoral Volume, PTBE And Edema Index

A total of 14 cases out of 30 patients showed presence of PTBE(Group A henceforth) while the rest of 16 cases did not show any presence of PTBE(Group B henceforth).

The mean tumor volume of 30 cases was approximately 265.07 cubic centimeters, while the mean tumor volume of group A & B separately was 428.57 & 122.00 respectively (Fig 1). This difference in the mean volumes was statistically significant (p<0.001).

Expression of Aquaporins

Out of total 30 cases, a total of 10, 13 and 3 (33.3 %, 43.3 % & 10 % respectively) cases exhibited expression of aquaporin 1, 4 & 9 respectively while 20, 17 & 27 (66.7 %, 56.7 % & 90% respectively) cases exhibited nil expression of aquaporin 1,4 & 9. Out of the cases which showed expression of various aquaporins, two cases showed expression of all the AQPs i.e 1,4 & 9. A total of 8 cases showed expression of AQP 1 & 4 while there was no expression of AQP 9 in these 8 cases. There was 1 case which showed expression of AQP 4 & 9 while no expression of AQP 1 was seen in this case. A total of two cases were only AQP 4 positive with nil expression of AQP 1 & 9 (table 1).

Correlation Of PTBE with AQPs

An approximately 64.2 % cases of Group A expressed AQP1 vis-a-vis only 6.2% cases of Group B (p<0.001; fisher's exact test). Approximately 35.7 % cases of Group A did not show expression of AQP 1 vis-a-vis 93.75 % cases of Group B (p<0.001; fisher's exact test) (Fig 2). 85.7 % of cases of Group A expressed AQP4 vis-a-vis only 6.2% cases of Group B (p<0.001). Only 14.2 % cases of Group A did not show expression of AQP 4 vis-a-vis 93.75 % cases of Group B (p<0.001) (Fig 2).AQP 9 expression was noticed in only 3 (10 %) cases out of total 30 cases. Although all these 3 cases had associated PTBE, rest of the 11 cases associated with PTBE did not exhibited expression of AQP9. Also none of the 16 cases without edema showed expression of AQP9.

Table 1: Correlation between AQPs and PTBE

		PTBE	
		Present	Absent
AQP 1	Positive	9	1
	Negative	5	15
AQP 4	Positive	12	1
	Negative	2	15
AQP 9	Positive	3	0

DISCUSSION

Intracranial meningiomas conventionally considered as benign tumors with good prognosis, can be atypical or malignant in nature occasionally. Apart from these atypical or malignant meningiomas, a considerable proportion of benign meningiomas are also known to be associated with poor outcomes in the form of greater morbidity pre and post surgery as well as higher rates of recurrence even though the pathology is benign.

Peritumoral brain edema (PTBE) in meningiomas has been studied quite extensively as PTBE has been known to be associated with poor prognosis in any intracranial pathology and meningiomas is no exception. Characteristically, it is the vasogenic edema which is seen to be associated with meningiomas. The unfavorable outcomes associated with PTBE are in the form of increasing incidence of brain herniations, technical difficulties during surgery and a higher rate of recurrence. The exact pathogenesis and mechanism of development of edema is not very clearly understood. Aquaporins (AQPs) are the water channels which have been recently implicated in the pathophysiology of development of PTBE.

This study was performed with the aim of studying the PTBE in cases of meningiomas and correlating it with various aquaporins (AQPs) (1, 4 & 9 namely).

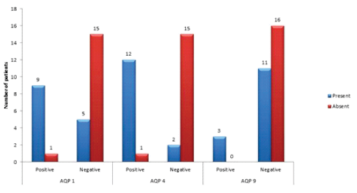

Figure 1 : Bar diagram showing correlation between PTBE and AQPs

Correlation between AQP 1, PTBE & other Factors

In brain, aquaporin 1 is known to be expressed in all the capillary

endothelial cells and is known to play a role in the production of CSF.[11,12] Very few studies have been done in respect of expression of AQP 1 in cases of brain tumors and even lesser in cases of meningiomas. Mitsuhiro et al. [13] studied expression of AQP 1 in mice rats by implanting glioblastoma cells and found it to be expressed heterogeneously depending on the cellular origin and the location of the tumor. Deb et al[14] reported expression pattern in cases of primary CNS tumors. They found that expression of AQP 1 was increased in cases of gliomas and ependymomas as compared to meningiomas however their study included 10 cases of meningiomas out of which only 1 case was associated with PTBE. Nagashima G et al[15]reported that AQP-1 was highly expressed at the dural attachment and invading front of meningioma and that this may indicate that dural invasion of the meningioma is facilitated by AQP-1-induced water flow and neovascularization. Similar observations were also made in our study with expression of AQP1 correlating with PTBE. An approx 64.2 % of cases with PTBE expressed AQP1 vis-a-vis only 6.2% cases without PTBE ($p<0.001$). Approx 35.7 % cases with PTBE did not show expression of AQP 1 vis-a-vis 93.75 % cases without PTBE ($p<0.001$).

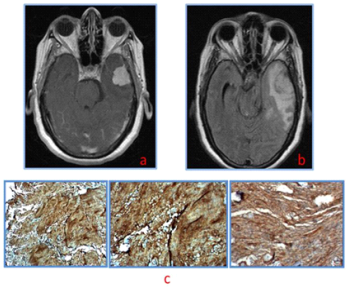

Figure 2: a & b: Post contrast and FLAIR axial

showing a well circumscribed, extra axial lesion noted along the anterior left temporal lobe. There is marked perilesional vasogenic edema **c:** Expression of all three markers i.e AQP 1,4 & 9

Correlation between AQP 4 and PTBE

AQP 4 in relation with meningiomas has been researched recently. Wang et al.[16] reported that the AQP4 expression was significantly higher in the edema group and a relationship between AQP4 and VEGF was also found. Ng WH et al.[6] also reported that aquaporins expression is increased in edematous meningiomas. Overexpression of AQP4 was associated with significant peritumoral edema. They further suggested that AQP4 overexpression can lead to abnormal water transport and edema formation in meningiomas and the inhibition of AQP4 water channels is a potential therapeutic option to reduce the adverse effects of peritumoral edema in meningiomas. Tan et al. and HU et al.[7,17] also reported that expression of AQP 4 was increased in edematous meningiomas. This study showed similar results with expression of AQP-4 correlating with PTBE. An approx 85.7 % of cases with PTBE expressed AQP4 vis-a-vis only 6.2% cases without PTBE ($p<0.001$). Only 14.2 % cases with PTBE did not show expression of AQP 4 vis-a-vis 93.75 % cases without PTBE ($p<0.001$).

Correlation between AQP 9, PTBE & other Factors

Few studies have been done correlating AQP 9 with brain tumors (mostly that of gliomas and astrocytic tumors). No study has been done correlating role of AQP 9 in factors affecting PTBE development in meningiomas. Tan et al. and Warth et al.[18,19] however have reported increased expression of AQP 9 in human brain gliomas and astrocytomas. Also, at molecular level, AQP 9 has shown to be involved in the energy metabolism and transport of solutes like lactate unlike AQO 4 which is involved in water transport and thus related to the presence or absence of brain edema.[20,21]

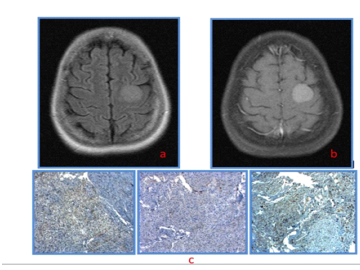

Figure 3 a & b: FLAIR and Post contrast axial showing a

well defined extraaxial mass lesion broad based to the dura in the region of the convexity of Lt high posterior frontal lobe. No edema was present **c:** No expression of any aquaporins

Findings in our study also supported above statement with no significant correlation found between PTBE and expression of AQP 9. AQP 9 expression was noticed in only 3 (10 %) cases out of total 30 cases. Although all these 3 cases had associated PTBE, rest of the 11 cases associated with PTBE did not exhibited expression of AQP9. Also none of the 16 cases without edema showed expression of AQP9. *This study was first to have incorporated three different types of aquaporins and correlating it with PTBE in meningiomas. Most of the studies in literature on meningiomas have correlated either with AQP 1 or AQP 4 with development of edema.*

To summarize, this study shows a trend of positive correlation between expression of AQP1 & AQP4 with presence of PTBE and thus suggests a promising role of AQP1 & 4 as a surrogate marker of prognosis as well as a possible therapeutic option in cases of meningiomas. However, no significant association has been found between AQP 9 expression and PTBE.

CONCLUSION

Expression of aquaporins 1 & 4 is associated with development of peritumoral brain edema in cases of meningiomas. No significant relationship was noted with the expression of aquaporin 9 and peritumoral brain edema. This finding may have an impact on the possible therapeutic target in improving the prognosis of intracranial meningiomas.

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