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The Role of Aquaporines in Brain Tumors

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1. Introduction

As about 80% of the brain is water, cerebral edema, associated with various cerebral injuries is critical and crucial events as the accumulation of excessive fluids will cause fatal cerebral herniation.
Water molecular channels called aquaporines (AQP) which are small membrane-spanning proteins which are expressed at plasma membranes[1,2], There are thirteen AQPs which are divided by three groups. Recently AQPs plays roles of cell migration[3] and proliferation[4]. In central nervous system, eight AQPs (1,3,4,5,6,8,9, and 11) are expressed. AQP4 is expressed in astrocytes and AQP1 in cholloid plexus, predominantly.
Recent researches elucidated the physiological roles of AQPs expands from water channels to other function associated with tumor biology. Firstly, AQPs were found in high grade malignant tumors[5,6]. And the expression of AQPs was correlated with metastatic potentials of malignant tumors and made easier to tumor cell migrations[3].
To elucidate the characterization of the expression of AQPs especially of AQP 1 and 4, and the relation of the expression of VEGF family and their receptors, we had investigated the expression of these proteins in various tumors of the central nervous system, immunohistochemically
In this review, we survey the physiological roles of AQP 1 and 4 in central nervous system tumor, using our data and recent reports.

2. Materials and methods

Thirty-one tumors and three cerebral tissue for control were used at our study until now[7,8] Astrocytomas were reclassified according to WHO classification[9] Although we could not examine the histology of primary tumors, the histological type of metastatic carcinoma was confirmed by the charts. Non-neoplastic cerebral tissue was obtained from three patients who underwent cerebral resection for cerebral hemorrhage. No information about corticosteroid treatment including dexamemethasone, was obtained in this study.

3. Immunostainings

Tissue specimen were immuunostained by ABC methods using antihum an AQP 1, antihum an AQP4 polyclonal antibody (H80, diluted 1:50;Santa Cruz Biotechnology, Santa Cruz, CA, USA), antihuman VEGF polyclonal antibody (C-1, diluted 1:1000: Santa Cruz Biotechnology) and antihuman MIB1-LI monoclonal antibody (diluted 1:100;DAKO, Kyoto Japan)

4. Results

In glioma, immunoreaction for AQP1 and 4 were recognized in tumor cells. Negative reactions for AQP 1 and 4 in tumor cells of grade 1 meningioma, medulloblastoma, neurocytoma, and lymphoma. Some of metastatic carcinoma cells — some of metastatic carcinoma cells were negative for AQP4 but a few tumor cells were positive for AQP1. Positive reactions for AQP 1 and 4 were recognized in reactive astroglia in the surrounded cerebral area of tumor. Immunoreactions for AQP 1 were recognized only endothelial cells in neovasculature of gliomas and grade 2 meningioms but normal endothelial cells negative for AQP 1 or 4. In grade 2 meningiomas, immunoreactions for AQP1 were detected in tumor cells and endothelial cells in neovasculature. A positive correlation of distinctiveness for immunoreactions between VEGF-A and C were obtained of expression of AQPs of endothelial cells in neovasculature.

5. Discussion

Recent researches elucidated the physiological roles of AQPs expands from water channels to other functions associated with tumor biology. Firstly, AQPs were found in high grade malignant tumors. And the expression of AQPs was correlated with metastatic potentials of malignant tumors and made easier to tumor cell migrations. AQP 4 was first cloned from rat lung[10], played major roles of pathogenesis of neuromyelitis optica[11].

In cerebral tissue, metastatic carcinoma show significant cerebral edema in the surrounded area. Reactive astrocytes show positive reactions for AQP1 and 4. The mechanisem of AQPs were still unclear., but As AQP4 did not alter blood-brain barrier integry or cerebral morphology[12] but deletion increased cerebral edema. Tail et al suggested the AQP4 played the elimination of cerebral edema using rat experimental SAH models[13].

AQP4 was massively up regulated in high grade astrocytoma and the expression of VEGF families tended to show a positive relation to AQP1 and 4 in high grade astrocytoma and grade 2 meningioma. Neovasculature in high grade astrocytoma and the adjacent areas of metastatic carcinoma showed glomeruoid proliferation of neovasculaturein which the physiological blood-brain barrier impaired, showing high VEGFs expression[14]. In meningiomas, significant peritumoral edema are associated frequently(50-92%)[15]. But a few studies are available for the expression of AQPs about meningioma, Ng et al. found increased expression of AQP4 with peritumoral edema in meningioma[6]. But all cases of menigiomas Ng et al studiesd were grade 1. No grade 2 or 3 meningioma was not included. Our report showed no expression of AQP4 in tumor cells of grade 1 meningiomas[5]. Cerebral edema in high grede glioma, metastatic carcinoma and meningioma was likely the result of the relationship between cerebral blood vessels and AQP4-mediated water transport.

AQP is expressed in the apical membrane of the choroid plexus and plays a role in forming CSF[16]But Marton et al. reported over expression of AQP 1 in atypical meningioma of infancy[17]. Nagashima et al suggested the dural invasion of meningiomas facilitated

Expressions of AQP1 played some physiological roles of cystic formation of cholloid plexus tumors[18]. As we describes, Nielsen et al reported that normal cerebral endothelial cells were negative for AQP1 but highly expressed in the endothelial cells of peripheral area of injuries, and cultured endothelial cells without astrocytes are also positive for AQP1. These data suggested that astrocytes endofeet may regulates adjacent endothelial cells in the endothelial cells in normal cerebral capillaries o switch off endothelial AQP 1 expression.

Our study could obtain the positive reactions of AQP1 in high grade glioma and grade 2 meningiomas but not in benign tumors.
In tumor biology, AQP1 deletion in mice reduceds tumor growth and migration of endothelial and astroglia[19]. The migration of cells are closely related tumor malignancy, The biological roles of AQP 1 for arachnoid cell differentiation were uncertain, but our results suggested AQPs played some roles of take a malignant potentials of meningiomas..
In this study we could not take no informations about cerebral edema. Furthers studies about the relations between cerebral edema and the expressions of AQPs of meningiomas are needed.

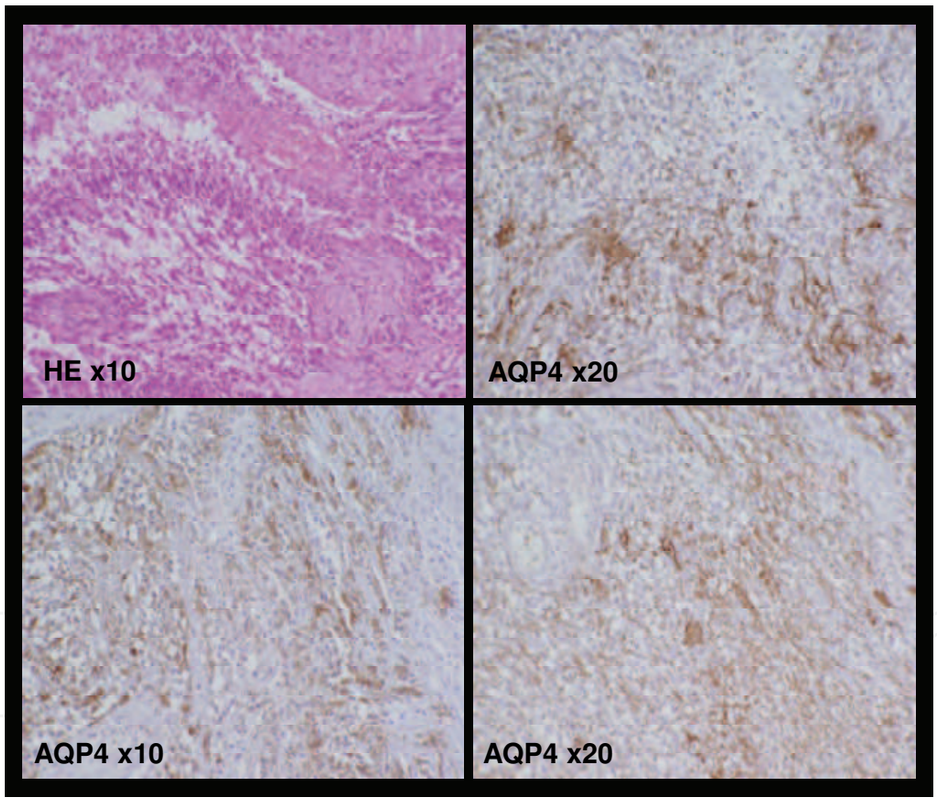

Fig. 1. Histological and immunohistochmeical findings of glioblastoma.
Histological findings (upper left) and immnunohistochemical staining for AQP4 (upper left and lower left and right). Positive findings for AQP4 are recognized in endothelial cells and tumor cells.

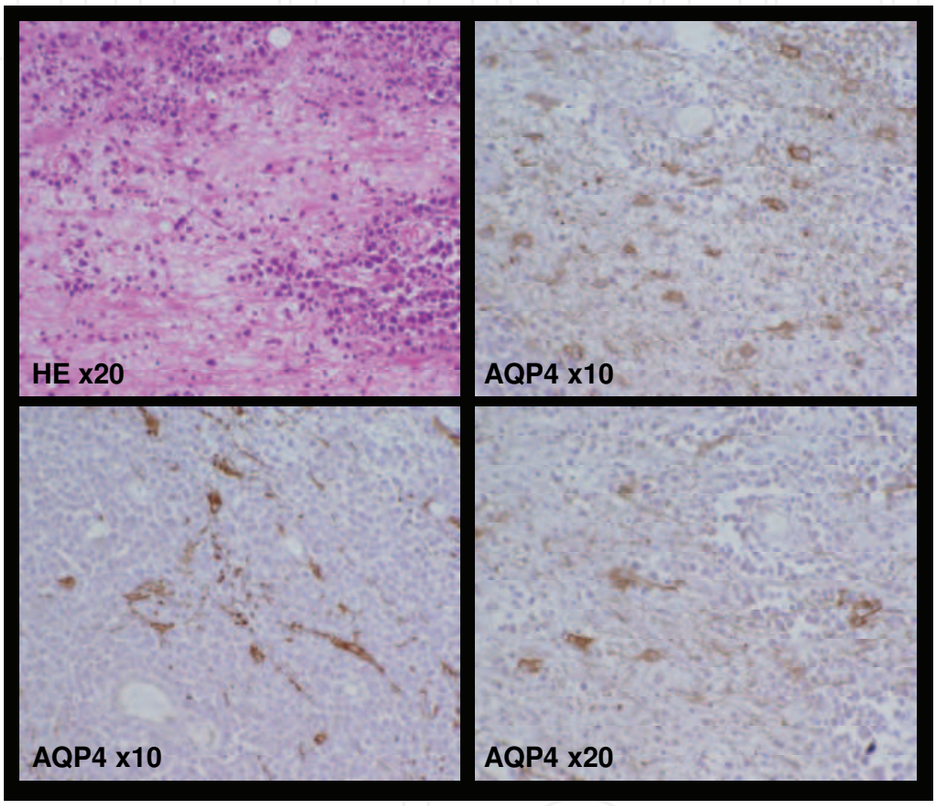

Fig. 2. Histological and immunohistochmeical findings of metastatic adenocrcinoma. Histological findings (upper left) and immnunohistochemical staining for AQP4 (upper left and lower left and right). Positive findings for AQP4 are recognized in endothelial cells and reactive astroglia.

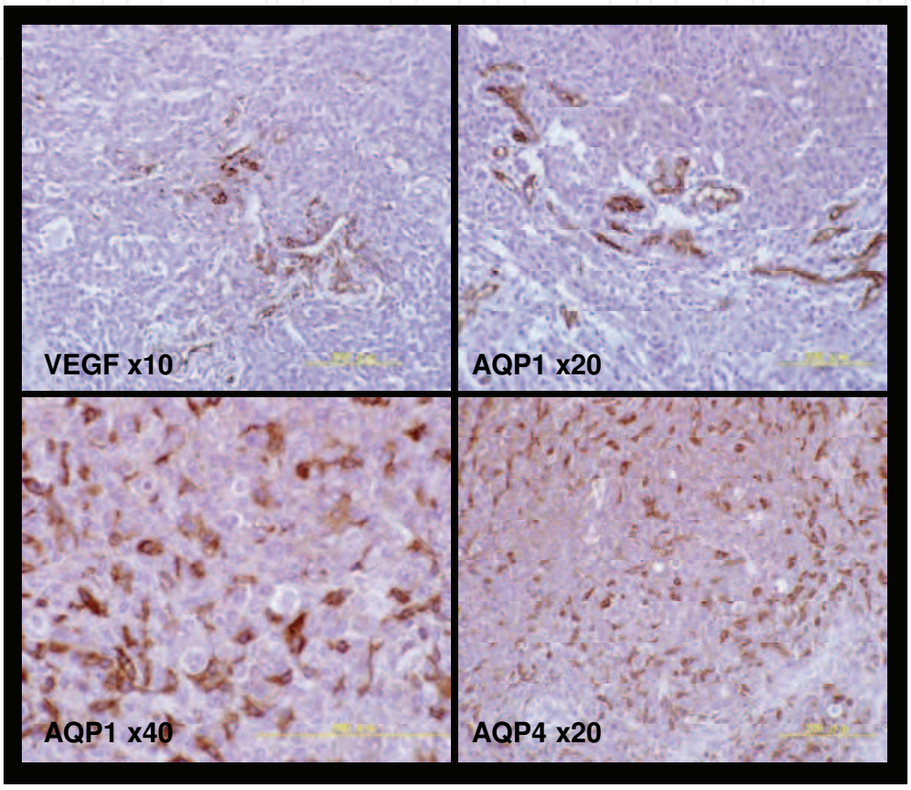

Fig. 3. Immunohistochemical findings of atypical meningioma.
Immunohistochmeical staining for VEGF (upper left), for AQP1 (upper right and lower left) and for AQP4 (lower right).
Positive findings for AQP4 in tumor cells and for AQP1 in tumor and endothelial cells are recognized.

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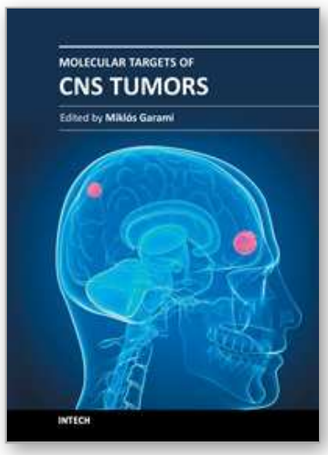

Molecular Targets of CNS Tumors

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Molecular Targets of CNS Tumors is a selected review of Central Nervous System (CNS) tumors with particular emphasis on signaling pathway of the most common CNS tumor types. To develop drugs which specifically attack the cancer cells requires an understanding of the distinct characteristics of those cells. Additional detailed information is provided on selected signal pathways in CNS tumors.

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