VEGF and Vasogenic Brain Edema in Meningiomas

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Abstract **Objective** To study the relation between vascular endothelial growth factor (VEGF) and vasogenic brain edema in meningiomas. **Methods** Sixty-one patients with supratentorial meningioma were selected for resection of the tumor. The specimens were evaluated pathologically and also classified in accordance with mac carty criteria. The presence and degree of vasogenic brain edema were studied by MR. The expression of VEGF was determined with immunohistochemical. **Results** 29 exhibited no edema or doubtful and 32 exhibited various degrees of vasogenic edema. The positive expression rate of VEGF in patients with edema was significantly higher than that of no edema or doubtful cases (χ^2=6.62, P<0.01). The expression rate of VEGF in patients with meningioma was 65.6%, in which, malignant meningioma accounted for 80.0%, meningotheliomatous meningioma, 75.0%, and fibroblastic meningioma, 37. 5%, respectively. A comparison of the former two and the latter one showed significant difference (χ^2=7.57, P<0.01; P=0.006). **Conclusion** VEGF may predispose vasogenic vasogenic cerebral edema in eningioma. The positive expression of VEGF may be used as an indicator for pathological classifications.

Key Words VEGF; meningioma; brain edema; magnetic resonance imaging

Most of meningioma is the benign tumor in the intracranial tumor, and about 40 %~60 % appear the brain edema in the peritumor. The edema induces the capacity increment and the ICP further increment. Also it makes the metabolism of the brain organization surroundings descendant. The concrete mechanism of the edema is still unknown. We try to study the VEGF of the meningioma to analyze the relation between the VEGF and the edema.

MATERIALS AND METHODS

Patients

61 patients with meningioma were collected from Shandong Qianfoshan hospital and Shandong Provincal hospital, with 4 relapse tumor and 57 primary tumor. There were 35 males with the mean age 56 and 26 females with the mean age 58.8. The tumors than 5cm in lengh were 38, and 23 cases were smaller. Also we have 8 cases surgical normal brain tissue specimen with 6 males and 2 females. In all of the selected tumor, 40 cases were meningothelia, 5 cases were malignant meningioma and 16 were fibrous type.

Materials

The method of the VEGF detection is streptomycete-avidin peroxydase linkage. In tissue slice the ratio of neoplastic cell coloration ⩽25% is defined as negative, and when >25%, defined is positive. We use MR technique to evaluate cerebral edema with T_2 weigh and measure gross tumor volume with T_1 weigh. And the volume of cerebral edema includes the gross tumor volume. Also we defined the edema level (Table 1) by the V:

V=the volume of cerebral edema-the gross tumor volume

Table 1 The levels of cerebral perilumoral edema

Level	V (cm)
Light edema	V⩽1.0
Midrange edema	1.0<V⩽2.5
Severe edema	V>2.5

Statistical Analysis

The chi square analysis and fourfold table exact propability was used for the statistical treatment.

RESULTS

VEGF positive staining is localized in the tumor

cell endochylema, and few are in the connective tissue. The positive cell is less and the staining is light when the cerebral peritumoral edema appeared lightly. The positive ratio of VEGF in the meningiomas is 65.6%, and in the malignant meningioma and meningothelia it is 80.0 % and 75.0% respectively. The positive ratio of the fibrous type is 37.5%. The comparison between the the malignant meningioma and meningothelia with the fibrous type has significant difference (χ^2= 7.57, P<0.01; P =0.006). The expression intensity of VEGH in the malignant meningioma is maximum, and the in fibrous type is minimum. Then we take the comparison between the malignant meningioma and the meningothelia and the expression ratio has no significant difference. (χ^2=0.44, P>0.05). In the normal brain tissue there is no VEGF expression in our experiments.

In all the selected cases, 29 cases have no edema or doubtful edema, and 32 cases have different extent edema. In the edema cases the VEGF expression significant(χ^2= 6.62, P<0.01). 7 cases with the VEGF negative expression have the edema surrounding the tumor, and 15 cases with VEGF positive expression show no edema surrounding. The sequence of the edema surrounding the tumor is malignant meningioma, meningothelia and the fibrous type from the severe to light in turns.

Also the results show the VEGF expression have nothing to do with the tumor size and the gender. The expression is concerned with the edema surrounding tumor, and it appears positive correlation tendency. (Table 2)

DISCUSSION

VEGF is a glucoprotein dimeride with the disulfide linkage, and has 4 molecule variations. The variations have the nearly equivalent effect in growing the vasopermeability and promoting vascular endothelial cell proliferation. The positive ratio of VEGF in the selected cases is 65.6%, and there is no VEGF expression in the normal brain tissue. The different patho-type meningiomas have the significant difference in the VEGF expression. The meningioma and meningothelia have the higher ratio, and the fibrous type is low. The VEGF expression have nothing to do with the tumor size and the gender. So VEGF can be used as one of the index for pathological classification. The higher expression of the VEGF in the meningiomas indicates that interruption of the VEGF signal pathway may prevent the tumor growing and the edema surrounds the tumor. Some studies show that the interruption of the VEGF function reduced the angiogenesis and slow the tumor growing.

The concrete mechanism of peritumoral edema has still not clear. And scholars had introduced some concepts just like the BBB (blood-cerebrospinal fluid barrier) adjacent the tumor being demolish, tumor oppression and tumor effectiveness. All this hypothesis had ignored the fact that meningioma is a focus of infection out of the brain. So meningioma itself can not bring about the edema. PG (prostaglandin), bradykinin, HT (histamine), oxyradical, PLA (plasminogen activator) etc. participate in the edema generation. But these factors have no exact statistical significance with the vaso-

Table 2 The relation between expression of VEGF and pathological parameters

Index	N	VEGF (+)	P
Tumor diameter (cm)			
≤5	23	16	
>5	38	24	>0.05
Peritumoral edema			
Yes	32	25	
No	29	15	<0.05
Edema level			
Light	11	5	
Midrange/severe	21	20	<0.01
Gender			
Male	35	21	
Female	26	19	>0.05

genic brain edema.

Meningioma is encased by the relatively non-permeated arachnoid, subarachnoid space and dura mater membrane, and separated from the normal brain tissue. Therefore, the meningioma correlated edema induced by the tumor vessels can not easily permeated into the intracranial peritumoral space. It shows great effectiveness on the formation of the intracranial edema that arachnoid is penetrated by the tumor to a certain degree. Though, there are no findings that peritumoral edema shows a relationship with statistical significance to any singal factor. Actually, VEGF may be a key element in the multifactorial etiology of the edema genesis. Meningioma achieves a large surface area in order to secrete some serum factors related to the edema, so it usually shows more invasiveness and can destroy the protein layer of the brain parenchyma. VEGF may also permeate into the brain cortex by the intracranial microcirculation and lead to the peritumoral edema directly. Out data indicates that the degree of peritumoral edema is concerned with the VEGF expression, but VEGF may not necessarily be the only reason for the peritumoral edema. Further research may include blocking the expression of VEGF at one or some points and then evaluating the situation of peritumoral edema. In group, there are 7 cases that negatively VEGF expressed with peritumoral edema formed, this means the generation of peritumor edema is a multifactor effect with VEGF plays an important role in it, also there are other biological–chemical active materials which influence the formation of peritumoral edema together with VEGF[7]. 15 cases in this show positive expression of VEGF with no edema formation, it suggests that some obstructive factor may exit in the process of the vasogenic brain edema formation, which can impede the competitive substance interact with the Ligand receptor and lock a certain step in the cascade cellular reaction after the combination of VEGF and transmembrane receptor.

Meningioma is really very common in the central nervous system, and it´s treated mainly by the resection. The concomitant brain edema of meningioma is disadvantage to the expose in the operation. Thus, the difficulty of the operation and the incidence of the postoperative complications is highly increased. Brain edema has already become a main reason for the physical disability and death of the meningioma patients. VEGF plays an important role in the formation of the peritumoral edema. The high level of VEGF expression suggests unfavorable prognosis and that the endotheliomatous or malignant meningioma may have greater possibility for the complicating of the brain edema than others. If the gene expression of VEGF is blocked, the inability of the expression can highly improve the therapeutic efficacy to the complications of the meningioma peritumoral edema, and decrease the fatality rate. As meningioma is abundant–vessels tumor, deep research of the relationship between the angiogenesis and the biological behavior may provide theory reference for the new therapy of meningioma.

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