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Research Article

Epidermal Growth Factor Receptor Expression Analysis in Different Racial Glioma Patients

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Abstract

Background

Vascular Endothelial Growth Factor (VEGF) represents a promising anti-neoplastic target. VEGF expression in same pathological grade of glioma in different ethnicities patients has not been integrated into clinical practice yet. The aim of our study is to investigate the relationship between VEGF expression level and prognosis in different ethnicities patients with glioma of an identical pathological grade.

Methods

We retrospectively analyzed VEGF expression level by immunohistochemical staining and prognosis in both Chinese Uygur and Han patients with glioma.

Results

The rate of positive expression of VEGF was 81.97% in 6l Han patients and was 60.61% in 33 Uygur patients with glioma. There was a significant difference between ethnicity and the VEGF expression (P=0.023). Regarding the impact of VEGF expression level on the prognosis of patients from the two ethnicities, the difference exerted an influence on the survival of patients with Low Grade Glioma (LGG) (P>0.05), which, however, was associated with the survival of patients with High Grade Glioma (HGG) (P<0.05).

Conclusion

VEGF expression differs in Han and Uygur patients with glioma. Ethnicity is one factor that has an effect on survival between Uygur and Han patients with HGG.

Keywords: Ethnicity; Glioma; Prognosis; Vascular endothelial growth factor

Introduction

Glioma is the most common primary tumors of the brain in adults [1]. The 5-year survival rate in patients with glioma is surprisingly low [2]. Conventional therapies play an important role in the treatment of malignant gliomas. However, the prognosis for patients with malignant gliomas still leaves much to be desired. In recent years, there have been some renewed efforts to develop the novel treatments based on molecular targets of glioma. The identification of these factors that can predict survival is an important goal for treatment of these patients, and a large number of studies have shown that the expression of VEGF was obviously related to the pathological grade of the tumor [3-7]. However, in a review of the literatures, no studies reported the association between VEGF expression level and different ethnic populations with an identical pathological classification. In this study, we compared the difference in VEGF expression level in glioma patients with identical classifications who settled in the Xinjiang province of China to elucidate whether ethnicity affects the VEGF expression and prognosis of these patients.

Material and Methods

Patients

This study was approved by the institutional ethical committee and involved 94 paraffin embedded tumor tissue specimens from the affiliated Tumor Hospital of Xinjiang Medical University from January 2005 to December 2010. There were 65 males and 29 females, including 61 Han cases and 33 Uygur cases. The inclusion criteria for the study were newly diagnosed cases without anti-tumor treatment. Patient characteristics were recorded consisting of ethnicity, age, gender, KPS scale, pathological grade and VEGF expression level. All samples were selected from individuals receiving routine treatment

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in our hospital with no history of other cancer and no symptoms of other forms of acute or chronic inflammation. The median age was 44 years (range 18~75). Based on the World Health Organization (WHO) classification of tumors of the central nervous system in 2000, there were 6 cases of grade I, 28 cases of grade II, 35 cases of grade III, and 25 cases of grade IV.

Methods

Tumor specimens were tested by immunohistochemistry for VEGF expression level using the Dako Epidermal Growth Factor Receptor (EGFR) pharm Dx assay™ (Dako, Denmark). VEGF expression level immunostaining score was calculated as the percentage of positively stained tumor cells and the staining intensity. A nucleus dyeing rate of 0~9% was marked as+, 10%~49% [2+] and >50% [3+] [8]. Both the percentage of positive cells and the staining intensity were evaluated under double-blind conditions. Two independent pathologists examined and scored each sample without any knowledge of the pathological outcome. The VEGF expression score was calculated as the percentage positive score × the staining intensity score and ranged from 0 to 9.

Statistical analysis

SPSS 20.0 was used in all statistical analyses. Numerical variables were summarized as an mean (standard deviation) or median (interquartile range). For comparison between the two groups, categorical variables were analyzed via the chi-square test. To elaborate the relationship between glioma VEGF expression level and pathological grades in the two ethnicities, the contingency table test was employed. Significance was defined as a P value of <0.05.

Results

VEGF expression level in Uygur and Han glioma patients

Positive VEGF expression rate in the tumor tissues in Han and Uygur glioma patients were 81.97% and 60.61%, respectively. When the positive rate of VEGF expression in the two groups was compared and analyzed, the expression difference was statistically significant (P=0.023). The VEGF expression level in Uygur patients was obviously lower than that in Han patients, which demonstrated that ethnicity can affect VEGF expression in glioma patients (Table 1).

Race	VEGF		Number
	Positive	Negative	
Han	50 (81.97%)	11 (18.03%)	61
Uygur	20 (60.61%)	13 (39.39%)	33
Total	70	24	94

Table 1: The positive rate of theVEGF expression in Uighur and Han glioma patients.

The correlation between the pathological grade and VEGF expression level in Han glioma patients

We analyzed the association between pathological grade and VEGF expression level in Han glioma patients. The result showed that the VEGF expression level in Han glioma patients was significantly related with tumor pathological classification (P=0.024) (Table 2).

Pathological Grade	VEGF Expression of Han Glioma Patients				Number
	Negative	+	++	+++	
Grade I	1 (50%)	1 (50%)	0 (0%)	0 (0%)	2
Grade II	2 (10%)	12 (60%)	5 (25%)	1 (5%)	20
Grade III	6 (26.1%)	5 (10%)	9 (21.7%)	3 (9.2%)	23
Grade IV	2 (12.5%)	3 (18.8%)	4 (25%)	7 (43.6%)	16
Total	11	21	18	11	61

Table 2: The correlation between pathologic grade and VEGF expression level in Han patients.

The correlation between the pathological grade and VEGF expression level in Uygur glioma patients

Table 3 displays the relationship between the pathological grade and VEGF expression level of 33 Uygur glioma patients. The results indicated that the VEGF expression level in Uygur glioma patients was not significantly different from the tumor pathological grade (P=0.683).

Pathological Grade	VEGF Expression of Uygur Glioma Patients				Number
	Negative	+	++	+++	
Grade I	1 (25%)	1 (25%)	2 (50%)	0 (0%)	4
Grade II	4 (50%)	1 (12.5%)	2 (25%)	1 (12.5%)	8
Grade III	4 (33.3%)	5 (41.4%)	2 (16.7%)	1 (8.3%)	12
Grade IV	4 (44.4%)	1 (11.1%)	4 (44.4%)	0 (0%)	9
Total	13	8	10	2	33

Table 3: The correlation between pathologic grade and VEGF expression level in Uygur patients.

Survival analysis between Uygur and Han glioma patients with identical pathological grade

In patients with grade I and II glioma, the median survival was62 months in Han people (22 cases) and 69 months in Uygur people (9 cases). There was no statistical difference between the two groups (P=0.125), namely, the survival time of LGG patients has no obvious relationship with ethnicity (Figure 1).

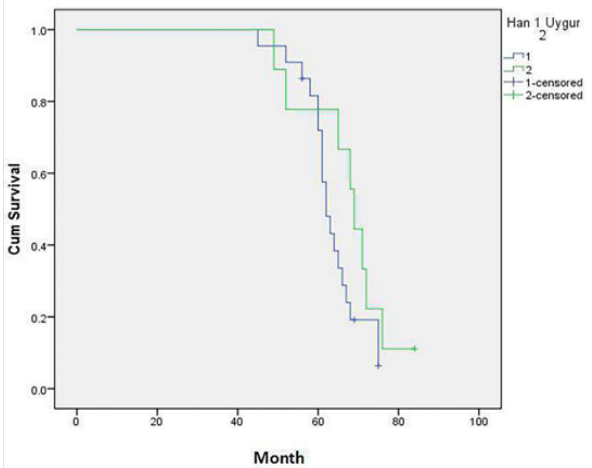

Figure 1: The survival timeshows no statistically significant difference between Uygur and Han glioma patients with low-grade glioma.

In glioma patients with grade III, the median survival was 16.2 months in the Han group (25 cases) and 28.7 months in the Uygur group (10 cases). There was a significant difference between the two groups (P=0.007). The average survival time of Uygur patients with grade III glioma was longer than that of Han patients (Figure 2).

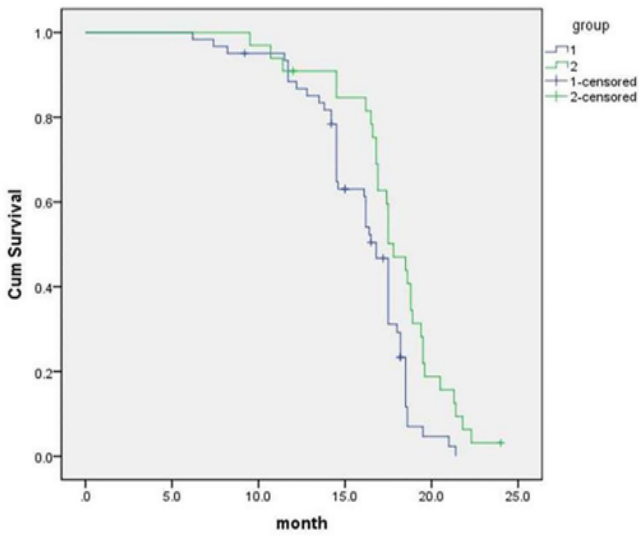

Figure 2: The survival timein Uygur patients is longer than that in Han patients with grade III glioma.

In patients with grade IV glioma, the median survival time was 11.8 months in the Han group (14 cases) and 17.5 months in the Uygur group (13 cases).There was a significant difference between the two groups (P=0.007). The survival time of Uygur glioma patients with grade IV glioma was longer that of Han patients (Figure 3).

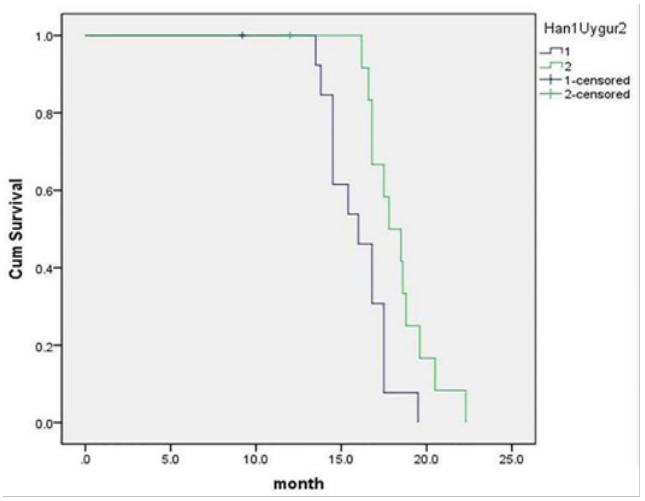

Figure 3: The survival timein Uygur patients is longer than that in Han patients with grade IV glioma.

Discussion

Vascular endothelial growth factor can induce angiogenesis, increase vascular permeability and promote division and proliferation of vascular endothelial cell [9]. VEGF also plays a key role in the process of tumor growth [10]. The vascular endothelial growth factor family of polypeptide growth factors regulates a family of VEGF receptor tyrosine kinases with pleiotropic downstream effects [4]. Angiogenesis is the best known of these effect Angiogenesis leads to new blood vessel formation and is implicated in both physiological and pathological situations [7]. The vascular endothelial growth factor family is the major mediator of this process. in patients with classical Hodgkin lymphoma (cHL), the level of VEGF-A, VEGFR-1 and VEGFR-2 was tested, only the expression of VEGFR-2 was positively correlated with serum albumin levels ≥4g/dL. No correlation with patient outcome was observed in CHL patients [4]. The T allele of VEGF +936C/T polymorphism is more common in primary tumors of the glioma, but there is no statistical relation with survival [5]. Angiogenesis commonly attributed to the anticrime and paracrine production of VEGF-A, which up regulates the VEGF signal transduction pathway, is a prominent feature of glioblastoma [11]. VEGF is secreted more in the glioma tissue than in normal brain tissue [12,13]. In recent years, the targeted molecular therapy of glioma based on VEGF as the target has gradually become a new strategy [14]. A large number of studies have indicated that VEGF expression level in glioma was closely related to the degree of malignancy of the tumor [15]. The higher the tumor pathological grade is, the higher the level of VEGF expression is [16,17]. Sometimes, The level of expression of some tumor related factors in tumors is closely related to the malignancy of tumors and the prognosis of tumors in Chinese just as Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-To-Lymphocyte Ratio (PLR) in the glioma, increased preoperative NLR and PLR are associated with worse OS, and NLR may be an independent risk factor to identify glioma patients with poor prognosis [18].

In the present study, we performed VEGF immunohistochemical staining on the embedded paraffin specimens. The positive rate of VEGF expression in Han patients was significantly correlated with tumor pathological grade, which was by and large consistent with other studies [19]. However, the difference was that positive VEGF expression rate in Uygur patients was remarkably lower than that in Han patients. Nonetheless, there was no obvious relationship between pathological grade in the Uygur glioma patients and the VEGF expression level, but the pathological grade was positively associated with VEGF expression level. We surmised that the negative result was possibly associated with the limited number of Uygur patients. Additionally, the VEGF expression level in HGG was distinctly high compared with that in LGG, which implied that the VEGF expression level may be considered as an index of the glioma grade.

When the ethnicity factor was analyzed for patients with gliomas of different pathological grades, there was no obvious difference regarding the role of ethnicity in the survival of LGG patients. However, this difference was evident between Han and Uygur patients with HGG. Thus, ethnicity is one factor impacting the survival in HGG patients.

Many studies confirmed that VEGF is highly expressed in tumor tissue. Xi observed that the rate of positive VEGF expression was positively correlated with pathological grade, the rate of the positive expression in the higher grade group was higher than that in the lower grade group and the rate of positive expression in the invasive cancer group was higher than that in the superficial tumor group in bladder cancer [20]. These findings indicated that the expression of VEGF might be associated closely with the invasiveness, metastasis and other

biological traits of bladder cancer. Some researchers discovered that the expression of VEGF in esophageal carcinoma was associated with lymphatic metastasis and the depth of invasion, and the expression was lower in para-carcinoma tissues than in esophageal cancer tissues [21]. Many scholars have put forward different opinions about whether the expression of VEGF was related to the clinical characteristics of endometrial diseases. For example, Abulafiao thought there was no correlation between vasculogenesis and the tumor grade, but Nakayama had the opposite opinion [22,23]. They considered that there was no correlation between angiogenesis and other clinical pathological parameters, and that angiogenesis was related to tumor grade, but some study found that Genetic variants were not associated with gliomas. Specific lifestyle habits and comorbidities stood out as independent risk factors for the disease. Low-grade gliomas showed an increase in patient survival with TMZ+RT treatment [24,25].

Similar ethnicity-related target expression was tested for other molecular targets such as the EGFR [7,26]. However, several phase III trials comparing EGFR inhibitor-gefitinib to placebo in advanced non small cell lung cancer patients demonstrated no improvement in overall survival in an unselected population [27,28]. Asian patients achieved a statistically significant improvement in overall survival with gefitinib. Regarding the mechanism, patients who benefited from gefitinib tended to harbor somatic activating mutations in the EGFR gene [29,30]. These data illustrated that molecular mutations could be used to identify subgroup of patients to differentiate VEGF expression in Han and Uygur patients. Additionally, initial studies that analyzed the efficacy of bevacizumab with recurrent glioblastoma explained its clinical activity, and first-line use of bevacizumab did not improve overall survival, although progression-free survival was prolonged [30]. As a result, we conferred that the VEGF expression level determined the response of bevacizumab and led to the different efficacy.

There was a significant difference in the correlation of VEGF expression level and tumor pathological grade between Xinjiang Uygur and Han patients with glioma. We reckon that the cause of the difference is due to ethnicity. Due to this inconsistency, further study in a large series is required to determine whether there is a difference in the curative effect of the molecular targeted therapy for glioma based on VEGF as the target in Xinjiang Uygur and Han glioma patients.

Conclusion

The present study reveals a significant difference in VEGF expression levels in glioma tissue between Uygur and Han glioma patients, although the number of patients in our series is limited and the monitoring method might be responsible for the difference in VEGF expression in glioma tissue. It is crucial to analyze the difference in efficacy of bevacizumab as a targeted VEGF inhibitor in Han and Uygur glioma patients in future.

Abbreviations

VEGF: Vascular Endothelial Growth Factor;

HGG: High Grade Glioma;

LGG: Low Grade Glioma;

EGFR: Epidermal Growth Factor Receptor.

Acknowledgment

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Conflict of Interest Statement

Authors state no conflict of interest.

Ethical Approval

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

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