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Original Article

The relationship between vascular endothelial growth factor and histological grade in intracranial meningioma

Rafael Contage Winter[1], Apio Claudio Martins Antunes[2], Francine Hehn de Oliveira[3]

[1]Neurosurgery Service, Hospital de Clínicas de Porto Alegre, Departments of [2]Neurosurgery and [3]Neuropathology, Hospital de Clínicas de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil.

E-mail: *Rafael Contage Winter - rwinter@hcpa.edu.br; Apio claudio Martins antunes - aantunes@hcpa.edu.br; Francine Hehn de oliveira - fholiveira@hcpa.edu.br

***Corresponding author:**
Rafael Contage Winter,
Neurosurgery Service,
Hospital de Clínicas de
Porto Alegre, Rua Ramiro
Barcelos, 2350/2040, Porto
Alegre-90035-903, Rio Grande
do Sul, Brazil.

rwinter@hcpa.edu.br

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ABSTRACT

Background: Meningioma is the most common benign intracranial neoplasm, accounting for 30% of all primary brain tumors. In 90% of cases, meningiomas are benign. Several aspects of molecular biology, including potential biomarkers, have been studied in attempts to better understand the natural history of meningiomas. Vascular endothelial growth factor (VEGF) is a biomarker responsible for inducing physiological and pathological angiogenesis. VEGF expression has been investigated as a potential predictor of several tumor aspects, including growth rate, recurrence rate, brain tissue invasion, peritumoral edema and surgical prognosis, and also as a marker of histological grade. However, there is no consensus in the literature with respect to the association between this biological factor and meningioma. We digitally analyzed immunohistochemical images using ImageJ software with the aim of correlating VEGF expression with tumor histology.

Methods: Tissue samples from patients presenting with meningioma who had undergone surgical removal between 2007 and 2016 at the Hospital de Clínicas de Porto Alegre (HCPA), in Southern Brazil, were analyzed to identify possible immunohistochemical associations between VEGF and histological grade and subtype.

Results: Seventy-six patients were included; 82% were female, mean age was 59.9 years (range: 18–91). No statistically significant associations were found between VEGF expression and histological grade or subtype ($P = 0.310$).

Conclusion: Our findings suggest that VEGF is frequently present in meningiomas regardless of histological grade and should not be used as a marker of severity or histological grade.

Keywords: Immunohistochemistry, Meningioma, Molecular biology, Vascular endothelial growth factor

INTRODUCTION

In 1922, Harvey Cushing coined the term meningioma to describe neoplasms arising from arachnoidal cells.[4] Up to 90% of these tumors are benign. They are rarely found in children and incidence increases with age.[23] In daily medical practice, they are often detected as incidental findings in imaging examinations performed for a wide range of diseases and indications.

Meningiomas can provoke a diverse set of symptoms, mainly depending on how they affect adjacent neurological structures, either by compression or irritation. Patients who are diagnosed with meningioma do not always need medical treatment. When indicated, the gold standard treatment is surgery, with total resection of the lesion including the involved dura (Simpson

Grade I resection).[35] Notwithstanding, radiosurgery is thought to have a good tumor control rate for meningiomas of a certain size.

Several factors related to the molecular biology of meningiomas have been studied as potential biomarkers for growth rate, likelihood of recurrence, malignant transformation, and invasion of adjacent brain tissue. Despite the considerable number of studies examining these factors, results remain conflicting and inconclusive.[1-3,5-12,14-22,24-30,32-34,37,38]

One such biomarker is vascular endothelial growth factor (VEGF),[12,19,30,32] a major inducer of physiological and pathological angiogenesis. Expression of VEGF in meningiomas is associated with peritumoral edema and leads to increased vascular permeability and microvessel density.[10,13,18,27-29] However, its relationships with recurrence rate, growth rate, and tumor grade remain controversial in the literature.

The present study aimed to determine the relationship between VEGF expression and tumor histology determined by digital analysis of immunohistochemical images using ImageJ™ software (NIH, USA).

MATERIALS AND METHODS

We analyzed tumor tissue samples from patients presenting with meningioma who had undergone surgery between 2007 and 2016 at the Hospital de Clínicas de Porto Alegre (HCPA), a university hospital in southern Brazil. Patients were included if they had not undergone preoperative embolization or been diagnosed with neurofibromatosis. The hospital's Research Ethics Committee approved this study under registration number 854.176 on October 28, 2014, and also waived the obligation to obtain informed consent from patients.

Hematoxylin and eosin (H and E)-stained slides were examined by a pathologist, and VEGF expression was analyzed immunohistochemically (ab1316, Abcam, USA, mouse monoclonal, clone VG-1, 1:2000 dilution). A BenchMark ULTRA automated platform was used to process samples (Ventana Medical Systems/Roche Diagnostics, USA), and ultraView Universal DAB Detection Kits were used to view reactions (Ventana Medical Systems/Roche Diagnostics, USA, catalogue no. 760-500).

Slides for immunohistochemical analysis were photographed under ×400 with an Olympus QColor5 camera (Olympus Corporation, Japan) coupled to an Olympus BX5 microscope (Olympus Corporation, Japan). The field photographed had been selected in advance by the pathologist. Images were digitally captured with QCapture software, version 2.81.0 (Quantitative Imaging Corporation, USA), using the same parameters for all slides and maintaining the same contrast settings for each sample. These images were digitally analyzed using ImageJ software, as described by Varghese, Bukhari, and Malhorta, based on Ruifrok's study.[31,36]

Statistical analysis

The results of the immunohistochemical analysis of VEGF expression were compared to tumor grade and histological subtypes. The sample size of 76 specimens was calculated considering a difference of 30% VEGF expression in relation to tumor grade, to achieve statistical power of 80% and a 5% significance level. Proportions were compared using Pearson's Chi-square test or Fisher's exact test. Results were considered significant if $P < 0.05$, and SPSS software, version 21.0, was used for the analyses.

RESULTS

The study sample comprised 76 patients, representative of a typical population of patients with meningiomas with respect to age, sex, and histological grade. The mean age of patients was 59.9 (SD = 15.6) years. The youngest patient was 18 years old and the oldest was 91. There were 62 women and 14 men.

A total of 76 tumors were assessed; 67 were Grade I (88.2%), 4 were Grade II (5.3%), and 5 were Grade III (6.5%) [Table 1]. Histological subtypes are shown in [Table 2]. VEGF expression was positive in 49 tumors (64.5%) and negative in 27 tumors (35.5%). Regarding histological grade, there were no statistically significant differences in VEGF expression

Table 1: Histological grades of the intracranial meningiomas in this sample.

Grade	*n*	%
I	67	88.2
II	4	5.3
III	5	6.6
Total	76	100

Table 2: Histological subtypes of the intracranial meningiomas in this sample.

Subtype	*n*	*n* (%)	VGEF + (%)
Angiomatous	1	1.3	100
Chordoid	1	1.3	100
Fibrous	18	23.7	52.6
Intraosseous	1	1.3	100
Meningothelial	33	43.4	68.6
Microcystic	2	2.6	50
Papillary	1	1.3	100
Rhabdoid	2	2.6	50
Transitional	17	22.4	70
Total	76	100	64.5

VEGF: Vascular endothelial growth factor

when Grades I, II, and III were compared ($P = 0.310$) [Table 3] or when low grade and high grade tumors were compared (Grade I vs. Grades II and III) ($P = 0.478$) [Table 4]. Certain epidemiological variables are listed in [Table 5], with the proportions of presence or absence of VEGF.

DISCUSSION

The natural history of meningioma is still unclear and course is unpredictable. Studies have employed molecular biology to search for factors that could be considered potential biomarkers of accelerated tumor growth rate, aggressive tumor behavior, and tumor grading and could, therefore, be used to guide more effective treatment in early stages and differential management of different tumor types.

New blood vessels develop to supply tumors through neoangiogenesis, which is a crucial process for tumor cell growth. Since VEGF is a major inducer of angiogenesis, VEGF expression is believed to be essential for tumor development.[1,9,11,21,30] For example, Ferrara and Davis-Smyth concluded that, in general, more aggressive tumors with higher grades and faster growth rates are associated with increased VEGF expression.[7]

Yamasaki *et al.* correlated VEGF expression with recurrence of Grade I meningioma after macroscopic total resection and found that high levels of VEGF expression were significantly associated with tumor recurrence, suggesting that this factor is one of the main predictors of recurrence.[38] Reszec *et al.* correlated expression of matrix metalloproteinase 9 (MMP-9) and VEGF in meningioma with peritumoral edema, and observed that VEGF was significantly associated with histological grade ($P = 0.001$).[29] In a cohort of 40 patients with meningioma, Sakuma *et al.* found that VEGF expression was related to development of peritumoral edema and to histological grade, thereby influencing the prognosis of patients.[32]

In contrast, and consistent with our findings, Baxter *et al.* prospectively assessed 175 patients and found no relationship between VEGF expression and histological meningioma grade.[3] This has also been described by other authors.[3,5,21,27,28] Pistolesi reported a potential relationship between specific VEGF isoforms and Grade I meningioma (isoform 189) and Grades II and III meningioma (isoforms 121 and 165), but found no statistically significant association between VEGF and histological grade.[26] Denizot *et al.* observed a relationship between VEGF and some histological subtypes in Grade I meningioma, but VEGF was not statistically associated with tumor grade.[5]

VEGF plays an important role in the neoangiogenesis of tumor cells, as demonstrated by several studies relating it

Table 3: Correlation between VEGF expression and histological grade (P=0.310).

VEGF	Meningioma grade			Total (%)
	I	II	III	
Negative				
n	28	0	2	27
% in VEGF	92.6	0	7.4	100
% in meningioma grade	37.3	0	40	35.5
Positive				
n	42	4	3	49
% in VEGF	85.7	8.2	6.1	100
% in meningioma grade	62.7	100	60	64.5
Total				
n	67	4	5	76
	88.1	5.3	6.6	100

VEGF: Vascular endothelial growth factor

Table 4: Correlation between VEGF expression and histological grade – high grade versus low grade (P=0.478).

VEGF	Meningioma grade		Total
	Low grade (I)	High grade (II-III)	
Negative			
n	25	2	27
% in VEGF	92.6	7.4	100
% in meningioma grade	37.3	22.2	35.5
Positive			
n	42	7	49
% in VEGF	85.7	14.3	100
% in meningioma grade	62.7	77.8	64.5
Total			
n	67	9	76
			100 (%)

VEGF: Vascular endothelial growth factor

Table 5: Histological grades and epidemiological variables for the sample against VEGF.

	VGEF		Total (*n*)	
	Positive	Negative		
Meningioma Grade				
Low grade	7 (9)	2 (9)	9 (76)	P=0.478
High grade	42 (67)	25 (67)	67(76)	
Sex				
Male	9 (14)	5 (14)	14 (76)	P=0.987
Female	40 (62)	22 (62)	62 (76)	
Skin Color*				P=0.321
White	47 (71)	24 (71)	71 (76)	
Black	0 (1)	1 (1)	1 (76)	
Brown	2 (4)	2 (4)	4 (76)	

VEGF: Vascular endothelial growth factor. *In Brazil, self-report skin color is used as a proxy for race/ethnicity, in line with national statistics office practice

to microvessel density in meningioma.[27,33,34] However, the relationship between VEGF expression and meningioma remains unclear. Although some studies have related VEGF expression to peritumoral edema,[13,27,34] the possible associations with histological subtypes and grades have not yet been well established.

We did not detect associations between VEGF expression and meningioma grade in our samples. Although VEGF is present in meningioma and is significantly involved in vascular development and central nervous system maintenance and repair, the effect most probably depends on other angiogenic factors.

CONCLUSION

VEGF and other factors of molecular biology have become essential to understanding the natural history of brain tumors, helping in the choice of appropriate treatment and follow-up decisions for patients presenting with meningioma. Our study suggests that there is no association between VEGF expression and meningioma grade. The limited sample size may be a contributing factor to the negative association and a very large sample size may be needed to detect associations. In view of the conflicting results reported in the literature, future studies with larger samples should focus on investigating the possible role of VEGF in tumor behavior.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Conflicts of interest

There are no conflicts of interest.

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