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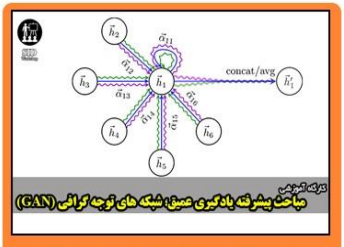

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The Association between Vascular Endothelial Growth Factor-related Factors and Severity of Multiple Sclerosis

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ABSTRACT

Previous studies have demonstrated that vascular endothelial growth factor (VEGF) can trigger angiogenesis as well as inflammation through binding to its membranous receptor-1 on endothelial and inflammatory cells. We aimed to correlate the circulatory number of cells expressing such receptor as well as the serum level of VEGF and the soluble form of its receptor-1 (sVEGFR1) to the severity of multiple sclerosis (MS).

This case-control study was done on 102 cases of MS lacking any other inflammatory or pathologic conditions and 75 healthy volunteer subjects. The severity of MS was examined by expanded disability status scale (EDSS). The serum levels of VEGF and sVEGFR1 were measured by ELISA, and the circulatory frequency of VEGFR1 expressing cells was counted by flowcytometry. Then, the correlation of these variables was evaluated by pearson's correlation coefficient and spearman's test. We also investigated the influence of sex, age, treatment duration, and the number of recurrences on such association through linear multivariate regression method.

We found an increase in circulatory level of VEGFR1 expressing cells and the serum level of VEGF as well as sVEGFR1 in MS patients compared to healthy controls (p<0.001). The greater severity of MS, the higher VEGFR1 expressing cells (ϱ=0.47; p<0.001), serum level of VEGF (ϱ=0.44; p<0.001), and sVEGFR1 (ϱ=0.76; p<0.001). Having adjusted the effects of VEGF on sVEGFR1, we found a significant association between the EDSS score and sVEGFR1 (β=0.007; p<0.001).

Our findings revealed that circulatory membranous as well as soluble expression of VEGFR1 increases during angiogenic and inflammatory phenomena of MS. Such increase may exacerbate the symptoms and cause more disability.

Keywords: Multiple sclerosis; Soluble VEGFR1; Vascular endothelial growth factor receptor 1

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INTRODUCTION

Multiple sclerosis (MS), as one of the most frequent neurologic diseases of young adults,[1] is a putative autoimmune disorder of the central nervous system (CNS). Clinically, it is characterized by recurrent episodes of neurologic dysfunction[2] resulting from lymphocytic infiltration to the CNS associated with activation of macrophages and microglia.[3] The pathologic hallmarks of MS are multiple perivascular foci of myelin sheath destruction in a perivenular distribution of inflammatory cells as well as reactive astrogliosis.[1] The perivascular relationship of MS lesions is considered to be important for the pathogenesis of the disease,[4,5] and in this regard, vascular endothelial growth factor (VEGF), as a heparin binding dimeric glycoprotein that induces the proliferation and migration of endothelial cells to form new vessels, increases the inflammation at least through penetration and extravasation of plasma macromolecules[6,7] and immune cells such as monocyte/macrophages.[8] Such roles may partly illustrate the pathologic role of VEGF in various inflammatory/autoimmune diseases such as systemic lupus erythematous, rheumatoid arthritis, and MS.[9] In the case of MS, VEGF acts as both angiogenic factor which disrupts blood-brain barrier (BBB)[10] and a chemotactic factor which in a VEGFR1 mediated pathway recruits circulatory monocytes,[3] therefore, it seems to have a significant role in MS-related immune reactions.

VEGF exerts its biological effects by binding to its surface receptors including VEGF receptor-1 (VEGFR1, also known as Flt-1) and VEGFR2 (also known as kinase domain receptor (KDR) or Flk-1) both belonging to the class III receptor-type tyrosine kinase (RTK) receptor family.[11] VEGFR1 affinity to VEGF is 7–10 times higher than VEGFR2,[12-15] and in this regard the chemotactic effects of VEGF are thought to be mediated through this receptor.[5] VEGFR1 mediated signaling in endothelial and non-endothelial immune/nonimmune cells is responsible for both regulating angiogenesis[16] and promoting VEGFR1 related pathologies such as cancer[17] and rheumatoid arthritis.[8]

To reveal the association of such factors in MS, previous studies demonstrated some evidences such as elevated serum VEGF level attributable to spinal plaque length,[9] overexpression of VEGF in MS and EAE plaques[18], and up regulation of VEGR1 in samples of normal appearing white matter from post-mortem MS brains.[19] Also, it has been shown that in MS plaques, macrophages outnumber T cells several folds and demyelination occurs in the proximity of macrophages rather than T cells.[20] On the other hand, there are some studies demonstrating decreased expression of VEGF level in MS plaques.[21] However, literature lacks the frequency of VEGFR1 expressing cells in MS through which - if their increased circulatory level be proved - we would have an extra antagonising treatment option. Moreover, having assessed the correlation of VEGF-related factors with disease severity, we would have an accessible diagnostic tool - blood sampling versus CNS sampling - as a laboratory criterion of disability in practice.

In order to further clarify the role of VEGF and the potential therapeutic role of its surface and soluble receptors, we measured the serum level of VEGF as well as its soluble recept-1 namely sVEGFR1, and circulatory frequency of cells expressing VEGFR1 in a group of MS patients and assessed their relationship to the severity of the disease.

MATERIALS AND METHODS

Study Subjects

Peripheral blood samples were simultaneously obtained from a total of 102 MS patients in remission phase being diagnosed according to clinical examination as well as MRI, and from 75 healthy controls being randomly selected from local blood donation organization in 2014. None of the patients suffered from any other autoimmune or inflammatory states; and no one took any immunomodulatory drugs. The Expanded Disability Status Scale (EDSS), the type of MS (CIS, RRMS, PPMS, SPMS, and PRMS), disease duration, treatment kind of the illness, and the number of recurrences were determined for each patient. Blood samples of all subjects were taken after signing the informed consent form approved by the local Ethical Committee. The study protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration.

Flow Cytometric Analysis and ELISA

At least one million fresh peripheral blood mononuclear cells (PBMCs) were separated from 2 ml of anticoagulated blood by Ficoll-Hypaque

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(Lymphodex, Inno-Train, Germany) density gradient centrifugation. VEGFR1 expressing cells were detected by staining with an anti-human surface VEGFR1-PE antibody (R&D Systems) for 1 hour at room temperature in the dark. 2×10^6 mononuclear cells in each sample were gated on the basis of light and side scattering properties and then at least 20,000 events were obtained to count anti VEGFR1-PE-stained target cells. PE-labeled IgG1isotype-matched control antibody was used to determine nonspecific binding. The percentages of such cells were analyzed by a 3-color flow-cytometry using BD FACSclibur Flow Cytometer and CELL Quest software version 3 (BD, USA). Serum levels of VEGF as well as sVEGFR1 were measured with commercial, sandwich type ELISA kits (eBioscience, USA) according to its instructions. Briefly, having prepared standard, blank, and sample wells, we orderly added 100 µl Biotin conjugate, diluted streptavidin-HRP, TMB substrate solution, and stop solution, among each of which we incubated all wells. After blanking microwell reader, we measured the colour intensity at 450 nm. The limit of detection of such VEGF and sVEGFR1 kits has been determined to be 7.9 pg/ml and 0.03 ng/ml, respectively.

Statistical Analysis

Data were expressed as mean ± SD. The statistical indices of VEGFR1 expressing cells and serum levels of VEGF as well as sVEGFR1 were analyzed using independent *t* and chi-square tests. Correlations between variables were calculated by Pearson's correlation coefficient and Spearman's test; and simultaneous effects of various factors on target cells were analyzed by linear multivariate regression method. EDSS score was normalized by logarithmic transformation. Adjusted R Squares were determined as a criterion of goodness-of-fit and they compared by Lr test. *p* values <0.05 were considered statistically significant. All analyses were performed using the STATA 10 and SPSS version 17 software.

RESULTS

Patients Characteristics and the Frequencies of the VEGFR1 Expressing Cells, Serum Levels of VEGF and sVEGFR1

Basic and clinical characteristics of both groups are shown in Table 1. Distribution of the frequency of VEGFR1 expressing cells and serum levels of VEGF as well as sVEGFR1 in both groups were normal. The least EDSS score was seen in the most benign type of MS namely CIS, and then it was increasing in more severe types of MS. The frequency of circulatory VEGFR1 expressing cells and the serum level of VEGF as well as sVEGFR1 in MS patients were significantly higher than those in healthy controls ($p<0.001$) (Table 1).

Association of the MS Severity with VEGF-related Factors

The frequency of circulatory VEGFR1 expressing cells and serum levels of VEGF as well as sVEGFR1 were different in MS patients according to EDSS score in such a way that they were significantly higher in severe forms of MS (EDSS=5-9.5) than those in mild forms (EDSS=0-4.5) ($p\leq0.04$)(Table 2).

Correlation of the Serum Levels of VEGF with sVEGFR1 and the Frequency of VEGFR1 Expressing Cells

There was a significant correlation between VEGF with sVEGFR1 (r=0.628, $p<0.001$)and the frequency of VEGFR1 expressing cells (r=0.383, $p<0.001$) (Table 3).Considering all variables of age, EDSS scores, number of recurrences, and disease duration in adjusted model, we found each unit increase in VEGF raised the serum level of sVEGFR1 as 0.23 units ($p<0.001$) ($R^2=0.61$) and the frequency of VEGFR1 expressing cells as 0.003 units ($p<0.001$) ($R^2=0.18$) (data not shown).

Association of the Serum Levels of VEGF, sVEGFR1 and the Frequency of VEGFR1 Expressing Cells with Severity of MS

All factors of VEGF, sVEGFR1, and the frequency of VEGFR1 expressing cells showed significant associations with EDSS score. Modeling such association separately, we showed that, among all predictor variables, only the variables of age and the number of recurrences remained in the final model (Table 4). However, according to Lr test, the sVEGFR1 seems to be a better predictor of EDSS than the VEGF and the frequency of VEGFR1 expressing cells. Predictor model could be shown as:

EDSS=-1.2+age×0.04+number of recurrences×0.13+sVEGFR1×0.007

Moreover, the correlation of the EDSS with sVEGFR1 ($p=0.76$) was more than that with VEGF ($p=0.44$) and frequency of VEGFR1 expressing cells ($p=0.47$).

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Table 1. Demographic and clinical characteristics of MS patients and controls

		MS patients	Healthy controls	*p* value
Number of subjects		102	75	-
Male/female		16/86	19/56	0.08*
Age (years) mean±SD		32.3±11.47	31.4±10.65	0.07**
Family history (%)	Positive	13	-	-
	Negative	89		
Disease duration (years) mean±SD		5.35±4.42	-	-
Treatment duration (years) mean±SD		2.75±3.16	-	-
Number of recurrences mean±SD		3.43±3.79	-	-
Number of patients in different types of MS	CIS	9	-	-
	RRMS	83		
	PPMS	1		
	SPMS	7		
	PRMS	2		
Number of patients using different kinds of drugs	Cinovex	82	-	-
	Rebief	11		
	Betaferon	2		
	Others	2		
	No drug	5		
EDSS (mean±SD)	CIS	1±1.06	-	-
	RRMS	2.1±1.5		
	PPMS	6		
	SPMS	4.9±1.43		
	PRMS	6.03±0.35		
VEGFR1 expressing cells±SD		3.41±1.69	1.85±0.99	<0.001**
Serum level of VEGF±SD		590.01±245.18	369.76±186.07	<0.001**
Serum level of sVEGFR1±SD		229.18±131.96	104.30±42.92	<0.001**

* Chi-square test **independent t-test

Table 2. The frequency of circulatory VEGFR1 expressing cells and the serum levels of VEGF as well as sVEGFR1 according to different variables in MS patients

		VEGFR1 expressing cells ±SD	VEGF±SD	sVEGFR1±SD
EDSS	Mild (0-4.5)	3.28±1.65	561.76±232.94	210.36±120.69
	Sever (5-9.5)	4.29±1.71	779.05±250.19	355.20±139.64
	p value*	0.04	0.002	<0.001
Type	Mild (CIS, RRMS)	3.34±1.68	561.84±232.82	210.35±116.40
	Sever (PPMS, SPMS, PRMS)	3.94±1.7	803.79±241.56	338.60±150.42
	p value*	0.295	0.003	0.002
Sex	Male	3.28±1.58	646.08±237.65	265.35±155.08
	Female	3.43±1.71	579.33±246.52	222.30±126.99
	p value*	0.735	0.321	0.234
Family history	Positive	3.34±1.81	537.45±260.64	222.87±113.32
	Negative	3.42±1.68	597.86±243.40	230.13±135.08
	p value*	0.877	0.410	0.854

*independent t-test

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Table 3. Correlation between serum levels of sVEGFR1as well as the frequency of VEGFR1 expressing cells with different variables in MS patients

	sVEGFR1		VEGFR1 expressing cells	
	Correlation coefficient	*p* value	Correlation coefficient	*p* value
VEGF	0.628	<0.001*	0.383	<0.001*
Age	0.268	0.008*	0.034	0.735*
EDSS	0.756	<0.001**	0.471	<0.001**
Number of recurrences	0.396	<0.001**	0.117	0.240**
Disease duration	0.382	<0.001**	0.114	0.257**
Treatment duration	0.217	0.031**	0.071	0.481**

*Pearson's correlation test **Spearman's rho test

Table 4. Separate linear multiple regression analysis evaluating the effect of VEGF, sVEGFR1, and the frequency of VEGFR1 expressing cells with the severity of MS

Variables	Coefficients			t	Sig. *p* values	Adjusted R Squared
	B	Std. error	standardized B			
VEGF	0.002	0.001	0.317	4.18	<0.001	0.49
Number of recurrences	0.179	0.036	0.381	5.01	<0.001	
Age	0.054	0.012	0.344	4.55	<0.001	
sVEGFR1	0.007	0.001	0.513	7.31	<0.001	0.61
Number of recurrences	0.130	0.032	0.277	4.04	<0.001	
Age	0.043	0.010	0.272	4.06	<0.001	
Frequency of VEGFR1 expressing cells	0.287	0.083	0.273	3.48	0.001	0.46
Age	0.052	0.012	0.337	4.37	<0.001	
Number of recurrences	0.177	0.037	0.378	4.85	<0.001	

DISCUSSION

VEGF has been shown to be a very potent stimulator of angiogenesis and also a pro-inflammatory marker implicated in the pathology of a myriad of diseases including autoimmune neurological inflammatory diseases[9,21-23] as well as tumours.[24,25] Having considered the angiogenic effects of VEGF, some investigators have reported new findings centring on vascular pathology as a determining factor in the immuno-pathogenesis of MS.[26] One simple explanation of this concept is that new blood vessels facilitate immune cell migration and increase their adhesion as well as cytokine production.[27] Breakdown of the BBB is also a significant event in MS lesions; and mechanistically, the capability of VEGF to down regulate claudin-5 and occludins, key components of tight junctions, promotes BBB breakdown in murine MOG-EAE.[10]

Mediating VEGF effects on the cellular level, VEGF receptors contributes to its inflammatory consequences especially via the transcription factor "nuclear factor of activated T-cells" (NFAT).[28,29] Not surprisingly, alterations in the VEGF/VEGFR system are observed in various inflammatory autoimmune diseases such as lupus erythematous, inflammatory bowel disease, psoriasis, rheumatoid arthritis and MS.[2] Understandably, yielding any pathology, such alterations in the amount of VEGF would negatively or positively be regulated by VEGFR. This might explain the reason of that increased level of VEGF in human rheumatoid arthritis[30-32] and also its correlation with the disease severity[33-35] that could be therapeutically inverted via a soluble form of the VEGFR1 (sFlt1) (which traps VEGF) in murine collagen-induced arthritis (CIA).[36] A recombinant version of natural sVEGFR1[37,38] as well as its adenovirus- or plasmid-mediated gene transfer[39] was shown to inhibit

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angiogenesis and inflammatory indices. In line with these concepts, antagonizing VEGF signalling has been effective in animal models of psoriasis,[40-41] rheumatoid arthritis[36] and MS.[23] Notably, antagonizing VEGFR-2, the main VEGF receptor, ameliorates murine acute MOG-EAE[23] which is well in line with a predominant anti-inflammatory mode of action of this treatment.

There are some varieties regarding VEGF and its related factors in MS. While VEGF serum levels have been reported to elevate during both remission and relapse phases,[9] VEGFR1 expression may decrease in chronic active MS lesions compared to normal white matter.[42] Also, examining CNS samples, the investigators have demonstrated that VEGF/VEGFR2 expression may consistently be up-regulated in both acute and chronic MS plaques (paralleled by an increased amount of microvessels) and also during the course of EAE in association with inflammatory cells.[18] Conversely, one study reported the down-regulation of VEGF in CSF mononuclear cells from MS patients and also astroglia of Lewis rats suffering from EAE.[21] The surprisingly multiple effects of VEGF in CNS has been reconciled, considering that VEGF splice variants could result in opposite effects due either to binding with different affinity VEGF-Rs and Neuropilin-1 or to differential tyrosine residue phosphorylation of VEGFRs.[43]

Our results showed higher circulatory number of VEGFR1 bearing cells and the serum levels of VEGF as well as sVEGFR1in a great number of MS patients than those in the control group. This may indicate potential pathogenic effect of VEGF and its related factors in MS. Furthermore, our data reveals that the higher numbers of such cells as well as such serum levels were associated with severity of the disease. This means that the effects of disease severity may act mainly via VEGF and VEGFR1 expression.

Showing a significant positive correlation between the VEGF and sVEGFR1 in our patients, we may consider that following VEGF increase in more severe types of MS, sVEGFR1 increases likely as a protective mechanism ameliorating the disease pathology. This concept may confirm the beneficial effect of sVEGFR1 which has recently been concerned as a novel therapy in autoimmune diseases like MS.[44] However, finding a strong correlation between EDSS and sVEGFR1 after adjusting the effects of VEGF, we showed that sVEGFR1 increases in severe forms of MS independently to VEGF.

Although we showed a significant association between the frequency of VEGFR1 expressing cells as well as VEGF with severity of MS, we found that sVEGFR1 may be a stronger predictor of MS severity in the presence of factors including age, sex, number of recurrences, and disease duration. Maybe other factors except the evaluated ones in our study may affect the MS severity which should be defined in other studies.

Studying the probable changes of VEGF-related factors in the underlying chronic inflammation of MS, we considered a homogenous population of the patients in remission phase. Obviously, such homogeneity renders more reliable findings in the absence of confounding factor of exacerbations. Our assessment also yields a simple practical application of such factors as clues of underlying severity for prognostic and at the same time therapeutic suggestions in an outpatient management. Actually, we recommend an easier as well as cheaper way to be taken in practice rather than CSF sampling as well as MRI which have already been done.

The limitation of our study was, firstly, lack of monitoring circulatory changes of VEGFR1 expressing cells and serum levels of VEGF as well as sVEGFR1 longitudinally. This limitation allowed just a cross-sectional analysis of such cell profiles of only limited robustness. Secondly, functional assays which provide further information on the immune status of the disease according to the serum levels as well as the number of such parameters were not performed.

Our findings reveal that VEGFR1 expressing cells and serum levels of VEGF/sVEGFR1 increase in MS patients as some angiogenic as well as inflammatory factors. Such increase was associated with MS severity; therefore, it may show exacerbating the symptoms and more disability. Considering such issue, we may use VEGF/VEGFR1 blockers as well as recombinant forms of sVEGFR1 to decrease the angiogenesis as a key method for treatment and decreasing the symptom and disability of MS.

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The authors have no conflicts of interest to declare.

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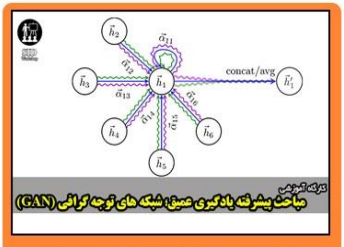

مباحث پیشرفته یادگیری عمیق؛
شبکه های توجه گرافی
(Graph Attention Networks)

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