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Vascular Endothelial Growth Factor: A potential diagnostic biomarker for major depression

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ABSTRACT

Despite intense research efforts undertaken by investigators throughout the world over the past half century to identify a specific biomarker for major depressive disorder (MDD), none have so far met the rigorous test of specificity, reliability and reproducibility. Vascular Endothelial Growth Factor (VEGF) has been implicated in the neurotrophic model of depression and several studies have assessed VEGF levels in depressed patients. The results have been discrepant largely due to design and assay differences among studies. The aim of this study was to assess plasma VEGF levels in a cohort of MDD subjects prior to treatment with psychotropic medication and compare them to those of healthy control (HC) subjects. Prospective study participants underwent extensive medical and psychiatric assessments before they were enrolled. Plasma concentrations of VEGF were measured by the technique marketed by Randox Technologies. The mean baseline VEGF for the healthy and depressed groups was 5.91 pg/ml (SD: 3.04) and 10.51 pg/ml (SD: 9.04), respectively, and this difference was statistically significant ($p = 0.001$). We detected a very low univariate relationship between VEGF and demographic and clinical variables. Using the Optimal Data Analysis a cut score of 6.64 pg/ml for baseline plasma VEGF distinguished depressed from healthy subjects with a 63% overall accuracy. We conclude these results support a role of plasma VEGF as a useful biomarker of depression that can be measured with a routine blood draw at the point of service. The specificity of this potential biomarker must be confirmed in studies that include other psychiatric disease entities.

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1. Introduction

1.1. Background

Vascular Endothelial Growth Factor (VEGF) has classically been described as an angiogenic mitogen produced by endothelial cells, and its role in maintaining vascular integrity has been extensively described (Leung et al., 1989). More recently, however, VEGF has been demonstrated to be widely expressed centrally and peripherally, and a number of studies have sought to describe its various roles in the brain. The psychiatric research community has focused attention on the potential relationship between VEGF and Major Depressive Disorder (MDD), a prime of a stress-related disorder. VEGF has been shown to be involved in hippocampal neurogenesis (Jin et al., 2002), to exert neuroprotective effects (Storkebaum et al., 2004) and to play an important role in the response to stress. In an animal model of chronic unpredictable stress, experimental animals had lower hippocampal levels of VEGF than control rats (Heine et al., 2005). VEGF also plays a role in the events of synaptic transmission (McCloskey et al., 2005), and influences hippocampus-dependent processes, such as learning and memory (Cao et al., 2004).

VEGF has been implicated in the neurotrophic model of depression, which is based on the finding that stress can cause a decline in levels of neurotrophins, such as Brain-Derived Neurotrophic Factor (BDNF) and VEGF. It is hypothesized that this decreased level of neurotrophins may cause atrophy of limbic structures that control mood, resulting in symptoms of depression. Furthermore, it is thought that antidepressant treatment may restore levels of neurotrophins and reverse this atrophy (Duman

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and Monteggia, 2006). However, VEGF levels in clinical data have not consistently supported the neurotrophic model of depression.

Several studies have assessed VEGF levels in depressed patients while other studies have assessed VEGF levels in response to antidepressant treatment. Unfortunately, results have been inconsistent. Peripheral levels of VEGF have been measured in different sample types, including human serum and plasma, as well as in epithelial precursor cells and leukocytes. No clear trend has yet emerged: four studies have found an increase in VEGF levels in depressed patients compared to healthy controls; four studies have found no difference, and one has demonstrated a decrease. However, methods employed vary greatly among studies, and many potential confounding variables were not adequately assessed (Clark-Raymond and Halaris, 2013).

1.2. Aim of study

The aim of this study was to assess plasma VEGF levels in a cohort of patients diagnosed with MDD prior to treatment with psychotropic medication and compare them to those obtained in a cohort of HC subjects. If prospective subjects met study criteria for inclusion, they were enrolled and subsequently received psychoactive medication for a 12-week treatment phase. Two separate cohorts of MDD patients were enrolled in two consecutively run studies of comparable design. In this paper we present baseline data from the entire cohort of MDD subjects who participated in either of the two treatment protocols. Treatment data will be reported in a future publication. The goal of the present study was to assess the potential role of VEGF as a biomarker of MDD, and obtain supportive evidence of its possible involvement in the pathophysiology of depression.

2. Material and methods

2.1. Study population

This study was approved by the Institutional Review Board of Loyola University Medical Center and was conducted according to the principles of the Declaration of Helsinki. Males and females between 20 and 65 years of age who met DSM-IV criteria for MDD, first episode or recurrent type, who were otherwise physically healthy and mentally capable to give informed consent, were considered as candidates. Their index episode had to be of at least 1 month duration and they could not have had psychopharmacological treatment over at least the preceding four weeks. A minimum score of 18 on their 17-item Hamilton Depression Scale (HAM-D17) was required for study admission. Additional exclusion criteria stipulated that subjects be free of any active source of inflammation including gum disease. Hypertension, dyslipidemia, diabetes mellitus, history of smoking or substance abuse in the preceding 6 months, and history of heart disease were exclusion criteria. Evidence of autoimmune disease was exclusionary. Female subjects could not be pregnant, lactating, or taking oral contraceptives. Since the study stipulated treatment with a psychoactive medication, sexually active female subjects had to agree to practice reliable contraception for the duration of the study. Screening blood samples (collected post-fasting) were obtained to ensure normalcy in complete blood count, complete metabolic panel, lipid profile, thyroid function and urinalysis (including pregnancy test). The presence of any clinically significant abnormalities excluded the prospective participant, leading to non-acceptance in the study and an alternative course of care. The presence of active suicidality and/or other Axis I diagnoses were also exclusion criteria. Seventy seven MDD patients met the inclusion/exclusion criteria after completing baseline evaluations and were enrolled in one of the two treatment studies. Unfortunately baseline VEGF values were available in 66 MDD subjects and only these subjects were included in the present analysis. Their demographic data is shown in Table 1.

2.2. Healthy control subjects

Eligible healthy control (HC) subjects were screened in much the same way as the MDD subjects, after providing written informed consent approved by the Institutional Review Board. They were enrolled only if the screening tests fell within normal range. Once deemed eligible, their baseline visit was scheduled soon thereafter and identical procedures were used as for the MDD group. The main exclusion criteria for HC subjects were any kind of medical or mental illness (including gum disease, substance use, mental illness or substance use amongst first degree relatives). Pregnant or lactating females were not included. Their HAM-D and BDI scores had to be less than 5 to be eligible. VEGF data were available for 21 HC subjects and their demographic data is shown in Table 1. HC subjects were recruited by word of mouth from the community and by posting flyers on the medical center campus. They were enrolled throughout the period the MDD subjects were recruited to avoid possible seasonal variation in VEGF levels. Every effort was made to match the age of patients and controls as closely as possible while maintaining a ratio of 3:1 (MDD vs HC subjects).

2.3. Study design

Two clinic screening visits (Screening-1 and -2) preceded all baseline measurements, a design which conveniently allowed for some acclimation to the clinic setting before the study procedures began. Screening visit-1 involved collection of blood and urine samples to obtain a complete blood count with differential, complete metabolic panel with electrolytes, thyroid function, lipid profile, hCG pregnancy test and a toxicology screen. Screening-2 involved a physical exam, inclusive of a gum exam, followed by a structured diagnostic interview and a battery of mood rating instruments: Mini International Neuropsychiatric Interview (MINI), Family History Questionnaire, Gynecologic History Questionnaire, Hamilton Rating Scale for Depression (HAM-D) and Anxiety (HAM-A), Beck Depression Inventory (BDI), Beck Scale for Suicide (BSS) and Clinical Global Impression (CGI). Demographic and past psychiatric history data was obtained from as many patients as possible at the initial screening visit but some data was never collected. In most cases the actual baseline visit occurred within a day or two after the second screening visit, unless the mandatory four-week antidepressant washout period had to occur first. If the subject had already been taking maintenance anti-anxiety and/or

Table 1
Demographics of patients with major depressive disorder and healthy control subjects.

	MDD subjects	Healthy control subjects	*p* value
Enrollment			
At Baseline	66	21	
Demographics			
Age (±SD)	41.3 (12.2)	38.9 (11.8)	0.43[a]
BMI (±SD)	30.3 (6.0)	25.9 (6.1)	0.005[a]
Weight in kg. (±SD)	84.4 (22.1)	74.0 (18.5)	0.06[a]
Female (Pre menopausal)	63.6% (83.3%)	66.7% (71.4%)	0.24[b] (0.33[b])
Caucasian	48.5% ($N = 32$)	57.1% ($N = 12$)	0.49[b]
Non–Caucasian	51.5% ($N = 34$)	42.9% ($N = 9$)	
Hx of Tobacco Use	Yes = 1	Yes = 2	0.18[b]
(not current use)	No = 45	$N = 19$	

[a] Two-sample *t* test.
[b] Chi-square test.

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