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Circulating Vascular Growth Factors and MRI Markers of Small Vessel Disease and Atrophy in Middle-Aged Adults

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Abstract

Background and Purpose: Little is known about associations between vascular growth factors and MRI markers in midlife. We investigated the association of serum Vascular Endothelial Growth Factor-1 (VEGF-1), Angiopoietin 2 (Ang2), soluble tyrosine kinase with immunoglobulin-like and EGF-like domains 2 (sTie2), and Hepatocyte Growth Factor (HGF) concentrations with MRI markers of brain aging in middle-aged adults.

Methods: We evaluated 1853 participants (mean age 46±9 years, 46% men) from the Framingham Heart Study. Serum growth factor concentrations were measured using standardized immunoassays. Outcomes included total brain, cortical and subcortical gray matter, white matter (WM), cerebrospinal fluid (CSF), and white matter hyperintensity (WMH) volumes derived from MRI; as well as fractional anisotropy in WM tracts from diffusion tensor imaging. We related VEGF-1, Ang2, sTie2, and HGF to MRI measures using multivariable regression models adjusting for vascular risk factors. We tested for interactions with APOE genotype and C-reactive protein. Results were corrected for multiple comparisons.

Results: Higher sTie2 was associated with smaller total brain (estimate by standard deviation unit ± se=−0.08±0.02, p=0.002) and larger WMH (0.08±0.02, p=0.002) volumes. Furthermore, higher Ang2 (0.06±0.02, p=0.049) and HGF (0.09±0.02, p=0.001) were associated with larger

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CSF volumes. Finally, higher Ang2 was associated with decreased fractional anisotropy, in APOE-ε4 carriers only.

Conclusion: Vascular growth factors are associated with early MRI markers of small vessel disease and neurodegeneration in middle-aged adults.

Keywords

Growth Factors; blood biomarkers; brain imaging; aging; C-reactive protein; APOE

Subject terms

Epidemiology, Lifestyle, and Prevention: Aging; Imaging and Diagnostic Testing: Magnetic Resonance Imaging (MRI); Basic, Translational, and Clinical Research: Growth Factors/Cytokines, Inflammation; Stroke: Cerebrovascular Disease/Stroke

Introduction

Midlife cardiovascular disease (CVD) and related risk factors increase the risk of abnormal brain aging and dementia.[1, 2] Vascular endothelial growth factor (VEGF-1), angiopoietin 2 (Ang2) and its soluble receptor Tie2 (sTie2), and hepatocyte growth factor (HGF) are involved in regulation of vascular function. Several cardiovascular risk factors have been associated with the concentration of these growth factors, and they have in turn been related to CVD.[3, 4] However, studies relating these growth factors to MRI markers of brain aging are lacking, particularly in middle-aged adults. Furthermore, these associations have not been investigated in the context of APOE-ε4, a strong genetic risk factor for Alzheimer's Disease (AD), or C-reactive protein (CRP), a marker of systemic inflammation.

This study explored the associations of circulating VEGF-1, Ang2, sTie2, and HGF concentrations with MRI markers of brain aging and evaluated effect modification by APOE-ε4 status or CRP concentrations in middle-aged adults from the Framingham Heart Study (FHS).

Materials and Methods

The data, analytical methods, and study materials are not currently available to other researchers for purposes of reproducing the results or replicating the procedure. The procedure for requesting data from the Framingham Heart Study (FHS) can be found at https://www.framinghamheartstudy.org.

We evaluated participants from the Third-Generation cohort of the FHS, with serum VEGF-1, Ang2, sTie2, or HGF, and brain MRI (n=1907). Participants with stroke, large cerebral brain infarcts or other neurological disorders were excluded (n=54, final n=1853).

This study was approved by the Boston University Medical Center Institutional Review Board and all participants provided written informed consent.

Standard immunoassays were used for measurement of serum growth factor concentrations. Brain MRI measurements included total brain, cortical and subcortical gray matter, white matter, cerebrospinal fluid (CSF), and white matter hyperintensity (WMH) volumes. Maps of fractional anisotropy (FA), a measure of white matter integrity,[5] were computed from Diffusion Tensor Imaging (DTI).

Multivariable regression models were used to relate growth factor concentrations to MRI outcomes. Models were adjusted for age, age^2, sex, time between blood draw and MRI, waist-to-hip ratio, systolic blood pressure, hypertension treatment, diabetes mellitus, current smoking, and prevalent cardiovascular disease. Secondary analyses tested for interactions between our predictors and APOE (ε4 carriers vs. non-carriers) or CRP concentrations (top quartile vs. bottom three quartiles) in MRI outcomes. Stratified analyses were adjusted for the same set of covariates described above. We applied False Discovery Rate (FDR) correction for multiple testing, using a $p<0.05$ threshold for main effects and $p<0.1$ threshold for interaction analyses. Further details are provided in Supplemental Methods (please see http://stroke.ahajournals.org).

Results

The study sample comprised participants aged 46±8 years (46% were men) with a low burden of CVD risk factors (Table 1).

Associations between growth factor concentrations and MRI outcomes are shown in Table 2. Higher concentrations of sTie2 were associated with higher WMH burden and lower total brain volume. Additionally, higher circulating Ang2 and HGF concentrations were associated with larger CSF volumes.

Voxel-based analyses revealed significant interactions between Ang2 and APOE genotype on FA. APOE subgroup analyses showed significant associations between Ang2 and FA in APOE-ε4 carriers. The Figure illustrates the corresponding significant regions, covering 36.08 mm^3 of the cerebral WM. The most relevant WM tracts included the posterior thalamic radiation (3.34 mm^3, p=0.0013), middle cerebellar peduncle (3.01 mm^3, p=0.0019), and cingulum (1.38 mm^3, p=0.0011). The full list of WM tracts is reported in Supplemental Table I (please see http://stroke.ahajournals.org).

Discussion

Our findings suggest that circulating growth factors involved in angiogenesis and blood vessel repair are cross-sectionally associated with MRI markers of small vessel disease and neurodegeneration as early as midlife.

We observed associations of higher circulating sTie2 with both greater WMH burden and smaller total brain volumes. sTie2 plays an important role in vascular biology and is elevated in CVD.[6] Additionally, sTie2 has a high affinity for Ang1, enabling higher concentrations of free Ang2, which promotes vascular destabilization and remodeling.[7] Disruption of the brain vascular wall may lead to leaky vessels, contributing to WM degeneration.[8] The association between higher Ang2 and larger CSF volumes is consistent with the findings observed for

sTie2. Furthermore, higher Ang2 is associated with decreased FA in APOE-ε4 carriers, suggesting that angiogenic factors may participate early in neurodegenerative processes, particularly in individuals at greater risk for AD.[9] We found that higher HGF is associated with increased CSF volumes. Elevated HGF concentrations have been observed as a response element to endothelial injury and in the presence of CVD.[10, 11] It is conceivable that increased HGF constitutes a marker of disease severity, or a biological response aimed to restore vascular health.

Strengths of our investigation include the use of data from a large community-based sample with MRI measures, vascular growth factors, and potential confounders and modifiers. Limitations include the use of CRP, a non-specific marker of inflammation,[12] and that our sample is primarily of European ancestry, limiting generalization to other races/ethnicities.

In conclusion, this study relates vascular growth factors to neurodegeneration and cerebrovascular disease as early as midlife. Future work will help determine the potential applications of these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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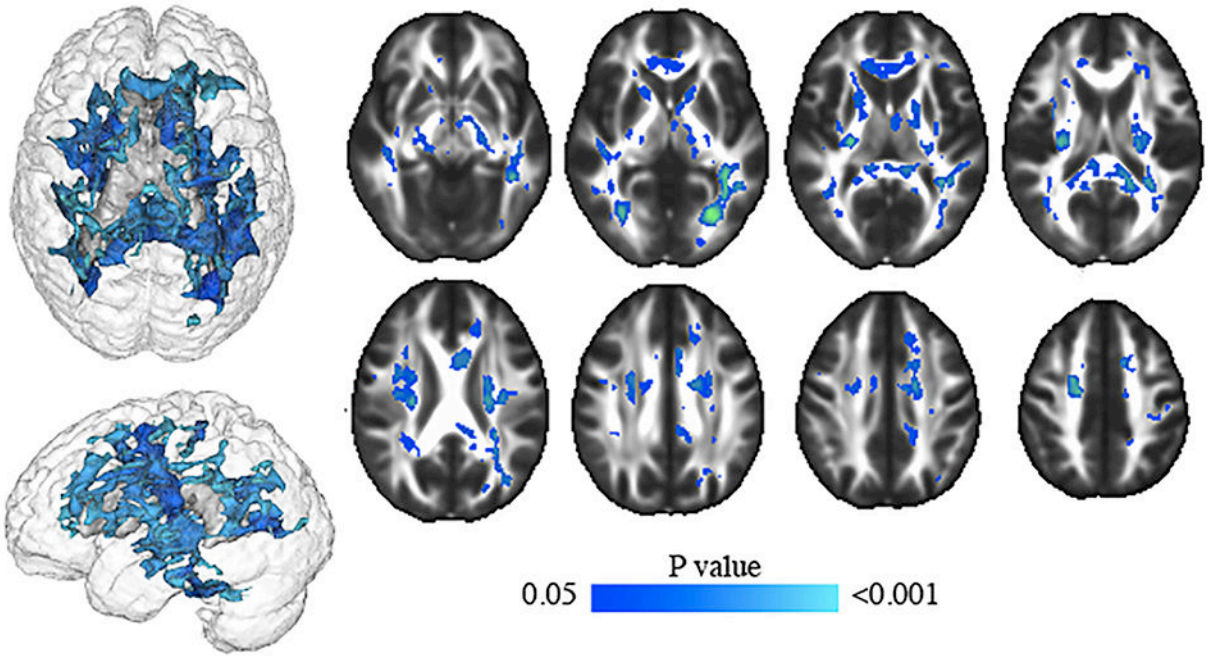

Figure. Associations between higher Ang2 concentrations and decreased fractional anisotropy among APOE-ε4 carriers

T-map of voxels showing a significant association between higher Angiopoietin 2 and decreased FA in APOE-ε4 carriers. Results were adjusted for cardiovascular risk factors and corrected for multiple comparisons.

Table 1.

Population characteristics

	N=1853
Men, n (%)	856 (46.2)
Age (y), mean (SD)	46.03 (8.48)
Systolic blood pressure (mmHg), mean (SD)	116 (14)
Antihypertensive medication, n (%)	329 (17.79)
Diabetes mellitus, n (%)	82 (4.43)
Current smoking, n (%)	164 (8.86)
Prevalent cardiovascular disease, n (%)	33 (1.78)
Waist/hip ratio, mean (SD)	0.91 (0.08)
Body Mass Index (kg/mt^2), median (Q1, Q3)	27 (24, 31)
CRP (μg/mL), median (Q1, Q3)	1.27 (0.61, 2.93)
APOE-ε4 carriers, n (%)	402 (22.72)
Blood draw to MRI interval (y), mean (SD)	7.59 (0.90)
VEGF-1 (ng/mL), median (Q1, Q3)	272.78 (154.84, 445.53)
Ang2 (ng/mL), median (Q1, Q3)	1.83 (1.38, 2.43)
sTie2 (ng/mL), median (Q1, Q3)	14.80 (12.39, 18.01)
HGF (ng/mL), median (Q1, Q3)	812.41 (696.37, 960.78)
MRI markers (cm^3)	
Total Brain, mean (SD)	1117.27 (118.6)
Total Intracranial, mean (SD)	1260.9 (126.13)
Cortical gray matter, mean (SD)	478.27 (48)
Subcortical gray matter, mean (SD)	145.45 (14.78)
White matter, mean (SD)	513.36 (62.96)
White matter hyperintensities, median (Q1, Q3)	1.27 (0.92, 1.72)
Hippocampus, mean (SD)	4.16 (0.72)
Cerebrospinal fluid, mean (SD)	302.63 (38.1)

Abbreviations: VEGF-1: vascular endothelial growth factor, Ang2: Angiopoietin2, sTie2: soluble tyrosine kinase with immunoglobulin-like and EGF-like domains 2, HGF: hepatocyte growth factor

Table 2.

Associations between growth factor concentrations and brain MRI measures

	VEGF-1 (β±SE)	Ang2 (β±SE)	sTie2 (β±SE)	HGF (β±SE)
Total brain	0.02±0.02	−0.02±0.02	**−0.08±0.02**†	−0.002±0.02
Cortical gray matter	0.03±0.02	−0.003±0.02	−0.05±0.02	−0.01±0.02
Subcortical gray matter	−0.01±0.02	0.02±0.02	−0.01±0.02	−0.05±0.02
White matter	0.01±0.02	−0.05±0.02	0.03±0.02	−0.02±0.02
White matter hyperintensities	−0.03±0.02	−0.004±0.02	**0.08±0.02**†	0.01±0.02
Hippocampus	−0.06±0.03	−0.03±0.03	0.05±0.03	−0.05±0.03
Cerebrospinal fluid	−0.03±0.02	**0.06±0.02***	−0.01±0.02	**0.09±0.02**†

Adjusted for age, age^2, sex, time between blood draw and MRI, waist-to-hip ratio, systolic blood pressure, hypertension treatment, diabetes mellitus, current smoking, and prevalent cardiovascular disease. β is estimate by standard deviation unit of log-transformed growth factor.

Abbreviations: VEGF-1: vascular endothelial growth factor, Ang2: Angiopoietin2, sTie2: soluble tyrosine kinase with immunoglobulin-like and EGF-like domains 2, HGF: hepatocyte growth factor

*p<0.05,

†p<0.005, FDR corrected p-values