Serum Placental Growth Factor as a Marker of Cerebrovascular Disease burden in patients with Alzheimer's Disease

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INTRODUCTION

- There is a high prevalence of mixed cerebrovascular diseases (CeVD) and Alzheimer's disease (AD) pathologies in the pathogenesis of dementia. Development of robust blood-based biomarkers provide critical tools to assess studies on diagnosis and treatments of AD with concomitant CeVD.
- Placental growth factor (PIGF) is a member of the endothelial growth factor (VEGF) family and a potent proangiogenic factor involved in regulating endothelial signaling and vascular function. PIGF levels in the CSF were found to be higher in AD and VaD patients, and they were associated with a higher CSF/plasma albumin ratio, WMH, and CMBs in PDD.[1,2] However, little is known about the alterations of peripheral PIGF levels in CeVD, cognitive impairment and dementia.
- The objective of this study was to to examine serum PIGF in preclinical stages of dementia and in AD, as well as to investigate its associations with concomitant CeVD and specific MRI markers of CeVD (i.e. cortical infarcts, WMH, lacunes, and CMBs).

METHODS

- A cross-sectional study was conducted in a total of 241 memory clinic participants who were clinically diagnosed as non-cognitively impaired (NCI), cognitively impaired no dementia (CIND), and Alzheimer's disease dementia (AD).
- All subjects underwent standard physical, clinical, blood tests, and neuropsychological assessments as well as neuroimaging scans at the National University of Singapore.
- Serum PIGF levels were measured with electrochemiluminescence immunoassays using the Roche Elecsys PIGF assay.
- Neuroimaging measurements of CeVD were determined by MRI. CeVD markers assessed include white matter hyperintensities (WMHs, measured by ARWMC scores), lacunes, cortical infarcts, and cerebral microbleeds (CMBs). Significant CeVD was defined using a previously established cut-offs as the presence of cortical infarct and/or ≥ 2 lacunes and/or confluent WMH (ARWMC score ≥ 8).[3]

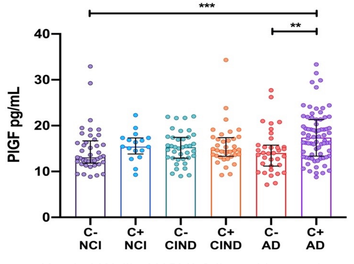
RESULTS

Table 1. Baseline characteristics of the participants based on cognitive categories

CHARACTERISTICS	NCI (N = 56)	CIND (N = 76)	AD (N=109)	P VALUE
Age, mean, y	68.4 (7.8)	74.1 (7.2)	76.7 (7.3)	**<0.001**
Female, no., %	34 (60.7)	39 (51.3)	80 (73.4)	**0.008**
Education ≤elementary, no., %	15 (26.8)	32 (42.1)	79 (72.5)	**<0.001**
APOE ε4 carrier, no., %	14 (25.0)	23 (30.3)	41 (37.6)	0.233
Hypertension, no., %	31 (55.4)	50 (66.7)	79 (72.5)	0.087
Diabetes, no., %	7 (12.5)	24 (31.6)	46 (42.2)	**0.001**
Cardiovascular diseases, no., %	3 (5.4)	10 (13.2)	13 (11.9)	0.316
Hyperlipidemia, no., %	34 (60.7)	57 (75.0)	79 (72.5)	0.172
PLGF, medium (IQR), pg/mL	14.5 (4.8)	14.8 (4.4)	16.1 (6.5)	**0.041**
MRI markers				
Presence of cortical infarcts, no., %	3 (5.6)	10 (13.5)	19 (18.1)	0.094
Presence of lacunar infarcts, no., %	4 (7.5)	7 (9.3)	18 (17.0)	0.146
Presence of CMBs, no., %	17 (30.9)	32 (42.1)	66 (61.7)	**<0.001**
ARWMC scale, median (IQR)	4.0 (5.0)	6.0 (6.0)	9.0 (6.0)	**<0.001**

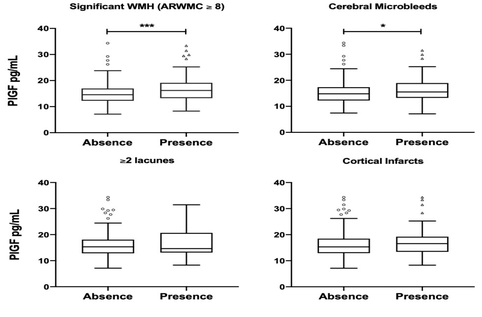
[a] p-value for group difference using one-way ANOVA with Bonferroni post hoc test, Kruskal–Wallis test with Dunn's post hoc tests or Chi-square tests.

Figure 1. Increased PIGF levels in AD with concomitant CeVD



Kruskal-Wallis ANOVA followed by pos-hoc Dunn's test was applied. Graph showing the median and IQR. Absence and presence of significant CeVD indicated as "C-" and "C+" respectively.

Figure 2. Associations between serum PIGF and specific CeVD markers



Bar graphs show medians and interquartile ranges (IQR). Mann-Whitney U tests were performed.

RESULTS cont.

Table 3. Multivariate regression analysis on the association between serum PIGF with WMH and CMBs.

PLGF (Log_2 normalized)	WMH by ARWMC scores β (95% CI)	Number of CMBs RR (95% CI)
All subjects (n=239)		
Model 1	**2.79 (1.48 – 4.10) p<0.001**	**3.28 (2.15 – 5.00) p<0.001**
Model 2	**1.55 (0.27 – 2.83) p=0.018**	**3.51 (2.21 – 5.55) p<0.001**
Model 3	1.23 (-0.02 – 2.47) p=0.053†	**2.20 (1.35 – 3.57) p=0.001‡**
Without dementia (n=131)		
Model 1	0.57 (-1.33 – 2.46) p=0.555	0.99 (0.50 – 1.96) p=0.979
Model 2	-0.35 (-2.15 – 1.44) p=0.699	1.38 (0.57 – 3.33) p=0.470
Model 3	-0.33 (-1.98 – 1.33) p=0.696 †	1.43 (0.59 – 3.47) p=0.428 ‡
AD dementia (n=108)		
Model 1	**3.37 (1.71 – 5.03) p<0.001**	**3.94 (2.17 – 7.17) p<0.001**
Model 2	**2.84 (1.10 – 4.59) p=0.002**	**2.85 (1.52 – 5.33) p=0.001**
Model 3	**2.69 (0.95 – 4.42) p=0.003†**	**1.99 (1.03 – 3.86) p=0.041‡**

Model 1: unadjusted
Model 2: adjusted for age, gender, hypertension, hyperlipidemia and cardiovascular diseases
Model 3: further adjusted for † CMBs or ‡ WMH.

CONCLUSIONS

- Serum PIGF has potential clinical utility as a biomarker for the presence of CeVD such as WMH and CMBs, in AD patients.
- Future longitudinal studies are needed to determine the utility of PIGF as a prognostic biomarker for cerebrovascular causes of cognitive impairment and dementia.

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