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Original Research Article

Retinal Vascular Fractals and Cognitive Impairment

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Key Words

Cognitive impairment · Retina · Microvasculature · Fractal dimension · Cognition

Abstract

Background: Retinal microvascular network changes have been found in patients with age-related brain diseases such as stroke and dementia including Alzheimer's disease. We examine whether retinal microvascular network changes are also present in preclinical stages of dementia. **Methods:** This is a cross-sectional study of 300 Chinese participants (age: ≥ 60 years) from the ongoing Epidemiology of Dementia in Singapore study who underwent detailed clinical examinations including retinal photography, brain imaging and neuropsychological testing. Retinal vascular parameters were assessed from optic disc-centered photographs using a semiautomated program. A comprehensive neuropsychological battery was administered, and cognitive function was summarized as composite and domain-specific Z-scores. Cognitive impairment no dementia (CIND) and dementia were diagnosed according to standard diagnostic criteria. **Results:** Among 268 eligible nondemented participants, 78 subjects were categorized as CIND-mild and 69 as CIND-moderate. In multivariable adjusted models, reduced retinal arteriolar and venular fractal dimensions were associated with an increased risk of CIND-mild and CIND-moderate. Reduced fractal dimensions were associated with poorer cognitive performance globally and in the specific domains of verbal memory, visuoconstruction and visuomotor speed. **Conclusion:** A sparser retinal microvascular network, represented by reduced arteriolar and venular fractal dimensions, was associated with cognitive impairment, suggesting that early microvascular damage may be present in preclinical stages of dementia.

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Introduction

An increasing amount of evidence suggests that vascular pathology is an independent and important contributor to the development of dementia including Alzheimer's disease and its preclinical stages [1]. In particular, cerebral small vessel disease has been associated with an increased risk of cognitive decline and dementia [2, 3]. Although modern neuroimaging modalities have contributed immensely to our understanding of microvascular pathology in dementia and cognitive impairment, it remains difficult to directly observe the cerebral microvasculature in vivo. As the retinal and cerebral microvasculatures share many anatomical and physiological aspects, the retinal microvasculature provides a viable window to directly observe changes to the cerebral one [4].

Thus far, studies have shown that traditional signs of retinal microvascular damage, such as retinopathy signs (e.g. retinal hemorrhage), are associated with both dementia and its earlier preclinical stages [5–7]. However, retinopathy signs are relatively late indicators of damage in the eye, and they indicate advanced stages of structural microvascular damage such as breakdown of the blood-retina barrier, and are hence not commonly seen. With recent advances in digital retinal imaging and analysis techniques, we are now able to objectively quantify the structure and pattern of the retinal microvascular network, which may reflect earlier and more subtle changes before the appearance of overt signs. Novel retinal vascular parameters such as fractal dimensions, which reflect the optimality of the vascular network, are of particular interest as they have recently been found to be associated with both stroke and dementia [8, 9]. In view of these associations with clinical disease, we hypothesized that these early retinal vascular network changes may also be present even in the preclinical stages of dementia. In this study, we examined the association between retinal vascular network parameters, particularly vascular fractal dimensions, and preclinical cognitive impairment in a Chinese population from Singapore.

Subjects and Methods

Study Population

The Epidemiology of Dementia in Singapore (EDIS) study recruits participants from the Singapore Chinese Eye Study (SCES), a population-based study of eye disease in Chinese aged 40–85 years. In order to efficiently utilize limited resources, it was decided to focus on those subjects who were most likely to have cognitive problems. Hence, in the first phase of the EDIS, SCES participants aged ≥ 60 years ($n = 1,538$) underwent screening using the Abbreviated Mental Test (AMT), a brief 10-question cognitive screening instrument previously validated in Singapore. Subjects with ≤ 6 years of formal education and an AMT score ≤ 6 , subjects with >6 years of formal education and an AMT score ≤ 8 or those for whom the subjects themselves or their main caregivers reported progressive forgetfulness were considered screening-positives. The screening-positive subjects ($n = 612$) were invited to take part in the second phase of the EDIS study, which included neuropsychological testing and brain magnetic resonance imaging (MRI). Details of the study methodology have been described elsewhere [10]. Of the 612 screening-positives, a total of 300 agreed to participate in the second phase from August 2010 to February 2012. Ethics approval for the EDIS study was obtained from the SingHealth Institutional Review Board and the National Healthcare Group Domain-Specific Review Board (DSRB). Written informed consent was obtained from all participants prior to recruitment.

Retinal Photography

Retinal fundus photographs were taken of each eye with a nonmydriatic digital camera after dilation of pupils with 1% tropicamide eye drops according to a standardized protocol for the participants as part of the SCES [11]. All retinal images from each participant were masked and collated for centralized grading at the Singapore Eye Research Institute. A semi-automated computer-assisted program, Singapore I Vessel Assessment (SIVA version 3.0.0.0), was used to assess retinal vascular fractal dimensions (among other parameters such as vessel caliber and vessel tortuosity) from optic disc-centered images of a randomly selected eye per participant [12, 13]. In brief, the program automatically detects and determines the optic disc radius and lays a grid over the area 0.5–2.0 disc diameters from the center of the optic disc. Vessels are also automatically detected and traced, creating a skeletonized image of the vascular network. Graders check that vessels have been accurately traced, and they remove any artifacts not part of the vessel network and manually correct any vessel path tracing errors. The retinal vascular dimension was separately evaluated for arterioles and venules, using the box-counting method [14]. As measures from both eyes are highly correlated to each other, a randomly selected eye was graded for each participant. Participants were excluded from analysis if vessel structures could not be visualized from retinal fundus images from both eyes.

Neuropsychological Assessment

Trained research psychologists administered cognitive testing to the participants in their habitual language. Brief cognitive screening tests included the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA) and the Informant Questionnaire on Cognitive Decline in the Elderly. Additionally, a formal neuropsychological battery (the Vascular Dementia Battery, VDB) previously validated for Singaporean elderly individuals was administered to all participants [15]. The following domains, using the respective neuropsychological tests in parentheses, were examined:

- executive function (Frontal Assessment Battery and maze task);
- attention (digit span, visual memory span and auditory detection);
- language (Boston Naming Test and verbal fluency);
- visual memory [picture recall and Wechsler Memory Scale-Revised (WMS-R) visual reproduction];
- verbal memory (word list recall and story recall);
- visuoconstruction [WMS-R visual reproduction, copy task, clock drawing and Wechsler Adult Intelligence Scale-Revised (WAIS-R) block design], and
- visuospatial speed (Symbol Digit Modalities Test and digit cancellation).

Additional details have previously been published [10]. Z-scores were derived for the individual subtests, and the scores for the individual domains were generated by summing up the Z-scores of each subtest under that domain and dividing the sum by the number of subtests. A final global composite Z-score was computed using all domain-specific Z-scores. Participants were considered to have failed a test if they scored lower than education-adjusted 1.5 standard deviations (SDs) below the established normal means on each individual test. Failure in at least half of the tests in each domain was considered as impairment in the domain.

Diagnosis of Cognitive Impairment and Dementia

Weekly consensus meetings were held with study clinicians, neuropsychologists, clinical research fellows, research coordinators and research assistants. Details from the clinical assessment, blood investigations, neuropsychological testing and MRI scans were reviewed. Noncognitive impairment (NCI) was diagnosed if participants were not impaired in any of the domains tested. Cognitive impairment no dementia (CIND) was defined as impairment in 1

or more domains in the neuropsychological test battery. CIND-mild was diagnosed if 1 or 2 domains were impaired, and CIND-moderate if more than 2 domains were impaired. Dementia syndrome was diagnosed in accordance with the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria. Participants who were diagnosed with dementia were excluded from the final analysis.

Assessment of Other Risk Factors

Data on demographic and vascular risk factors including age, sex, smoking, hypertension, diabetes, hyperlipidemia, height and weight were collected using a detailed questionnaire. The blood tests comprised a full blood count, random blood glucose and serum lipids including total cholesterol. Systolic and diastolic blood pressures were measured using a digital automatic blood pressure monitor (OMRON-HEM 7203; Japan) after resting for 5 min. The mean arterial blood pressure was calculated as two-thirds of the diastolic blood pressure plus one-third of the systolic blood pressure. The participants were categorized into nonsmokers and ever-smokers (past and current smokers). The BMI was calculated as the weight in kilograms divided by the height in meters squared.

MRI was performed on a 3-tesla Siemens Magnetom Trio Tim scanner, using a 32-channel head coil, at the Clinical Imaging Research Centre of the National University of Singapore. The scans were graded by 1 radiologist and 2 clinicians blinded to the neuropsychological and clinical data for the presence of stroke and cerebral microbleeds (Brain Observer Microbleed Scale) [16]. White matter lesion (WML) volume, total brain volume and total intracranial volume were quantified by automatic segmentation at the Erasmus University Medical Center Rotterdam, The Netherlands. Brain tissue segmentation was quantified by proton density-weighted T1- and T2-weighted imaging, whereas the WML volume was segmented using FLAIR [17–19]. The ratio of total brain volume to total intracranial volume was used as a marker of cerebral atrophy.

Statistical Analysis

For the comparison of baseline demographics and risk factors between the participants with gradable and those with ungradable retinal fundus images, and between the different diagnostic groups, Pearson's χ^2 test was used for categorical variables with independent t tests, and analysis of variance for continuous variables. Multinomial logistic regression models were constructed to calculate odds ratios (ORs) and their 95% confidence intervals (CIs) for CIND-mild and CIND-moderate per SD increase or decrease in retinal vascular parameters. The models were first adjusted for age and sex, then additionally for the risk factors of education level, socioeconomic status, mean arterial blood pressure, fasting blood glucose, serum cholesterol, smoking status and brain MRI markers. Similarly, adjusted linear regression models were also constructed for the Z-scores from the individual domains and the composite Z-score for all domains (VDB composite score) to test for linear relationships between retinal vascular parameters and cognitive performance. All statistical analyses were performed using SPSS version 17.0 (SPSS Inc., USA).

Results

Of the 300 Chinese participants recruited to the EDIS study, 7 participants diagnosed with clinical dementia were excluded. Of the remaining 293 participants, the 25 participants additionally excluded from the analysis (due to poor retinal image quality) were similar in their baseline characteristics to the included participants, except for education level (fewer with primary education and above, $p = 0.045$), socioeconomic status (lower, $p = 0.006$) and

Table 1. Baseline characteristics of the participants by diagnosis of cognitive impairment and dementia

	NCI (n = 121)	CIND-mild (n = 78)	CIND-moderate (n = 69)	p
<i>Demographics and general characteristics</i>				
Female, n	53 (43.8%)	42 (53.8%)	47 (68.1%)	<i><0.005</i>
Age, years	67.3±4.8	71.1±6.3	74.1±5.4	<i><0.001</i>
Above primary education, n	110 (90.9%)	61 (76.9%)	41 (59.4%)	<i><0.001</i>
Low socioeconomic status, n	58 (48.7%)	52 (71.2%)	57 (83.8%)	<i><0.001</i>
BMI	23.9±3.2	23.8±3.3	24.5±4.1	0.456
Systolic blood pressure, mm Hg	146.3±19.1	145.4±17.9	149.1±21.6	0.477
Diastolic blood pressure, mm Hg	78.9±10.1	75.2±10.1	74.8±10.9	<i><0.010</i>
Hypertension, n	88 (72.7%)	59 (75.6%)	61 (88.4%)	<i><0.040</i>
Random blood glucose, mmol/l	6.41±2.50	6.61±3.09	6.65±2.44	0.810
Diabetes, n	26 (21.5%)	19 (24.4%)	22 (31.9%)	0.278
Serum total cholesterol, mmol/l	5.32±1.01	5.06±0.97	5.33±1.05	0.493
Hyperlipidemia, n	67 (55.4%)	48 (61.5%)	48 (69.6%)	0.154
Ever-smokers, n	35 (28.9%)	24 (30.8%)	22 (31.9%)	0.906
MMSE score	27 (26–28)	25 (23–27)	21 (18–23)	<i><0.001</i>
MoCA score	24 (22–26)	20 (18–23)	16 (12–18)	<i><0.001</i>
<i>MRI markers</i>				
Presence of stroke, n	5 (4.1%)	14 (17.9%)	21 (30.4%)	<i><0.001</i>
Presence of cerebral microbleed, n	33 (27.3%)	24 (30.8%)	23 (33.3%)	0.510
WML volume, ml	1.38 (0.38–3.57)	1.79 (0.48–4.74)	3.26 (1.00–11.1)	<i><0.002</i>
Total brain volume/intracranial volume, ratio	0.820±0.018	0.817±0.018	0.812±0.018	<i><0.013</i>

Values denote means ± SD or medians with IQR in parentheses unless specified otherwise. The χ^2 test was used for categorical variables and Student's t test for continuous variables. The Kruskal-Wallis test was used for WML volume, MMSE score and MoCA score. Significant p values are set in italics.

Table 2. Age- and sex-adjusted associations of retinal vascular parameters (per SD decrease) with global cognitive performance and with diagnosis of cognitive impairment status

	Age- and sex-adjusted associations (n = 268)		
	composite VDB score, B ^a (n = 267)	CIND-mild, OR ^b (n = 78)	CIND-moderate, OR ^b (n = 69)
Caliber			
Arteriolar ^c	0.072 (–0.091 to 0.234)	0.70 (0.39–1.24)	0.81 (0.43–1.53)
Venular ^c	–0.080 (–0.240 to 0.081)	0.99 (0.57–1.72)	1.17 (0.63–2.16)
Fractal dimension			
Arteriolar	<i>–0.165 (–0.247 to –0.073)</i>	1.37 (0.99–1.89)	<i>1.73 (1.19–2.53)</i>
Venular	<i>–0.151 (–0.242 to –0.061)</i>	<i>1.38 (1.00–1.90)</i>	<i>1.79 (1.24–2.60)</i>
Tortuosity			
Arteriolar	<i>–0.143 (0.053 – 0.234)</i>	0.86 (0.63–1.17)	0.73 (0.51–1.05)
Venular	0.073 (–0.017 to 0.164)	0.90 (0.67–1.23)	0.85 (0.60–1.22)

Significant associations are set in italics. ^a Expressed as mean differences in normalized test scores with 95% CIs in parentheses. ^b Expressed as ORs with 95% CIs in parentheses. ^c Adjusted additionally for other vessel caliber.

Table 3. Multivariable-adjusted associations of retinal vascular parameters (per SD decrease) with global cognitive performance and with diagnosis of cognitive impairment status

	Model 2 ^a (n = 244)			Model 3 ^b (n = 243)		
	composite VDB score, B ^c (n = 244)	CIND-mild, OR ^d (n = 66)	CIND-moderate, OR ^d (n = 62)	composite VDB score, B ^c (n = 243)	CIND-mild, OR ^d (n = 66)	CIND-moderate, OR ^d (n = 61)
Fractal dimension						
Arteriolar	<i>-0.119 (-0.200 to -0.037)</i>	1.40 (0.98–2.01)	1.86 (1.20–2.88)	<i>-0.103 (-0.187 to -0.020)</i>	1.46 (1.01–2.12)	1.86 (1.17–2.93)
Venular	<i>-0.108 (-0.190 to -0.026)</i>	1.52 (1.05–2.21)	2.09 (1.35–3.22)	<i>-0.109 (-0.191 to -0.028)</i>	1.54 (1.06–2.25)	2.15 (1.38–3.34)
Tortuosity						
Arteriolar	0.072 (-0.010 to 0.315)	0.95 (0.66–1.36)	0.82 (0.53–1.25)	0.063 (-0.019 to 0.144)	0.93 (0.65–1.34)	0.82 (0.53–1.27)

Significant associations are set in italics. ^a Adjusted for age, gender, race, educational level, low socioeconomic status, mean arterial blood pressure, random blood glucose, total cholesterol and presence of stroke. ^b Adjusted for age, gender, race, educational level, low socioeconomic status, mean arterial blood pressure, random blood glucose, total cholesterol, presence of stroke and cerebral microbleeds, total WML volume and total brain volume/intracranial volume ratio. ^c Expressed as mean differences in normalized test scores with 95% CIs in parentheses. ^d Expressed as ORs with 95% CIs in parentheses.

Table 4. Associations between retinal vascular fractal dimensions (per SD decrease) with specific cognitive domain scores

	Executive function	Attention	Language	Visual memory	Verbal memory	Visuoconstruction	Visuomotor speed
Arteriolar fractal dimension							
Model I ¹	-0.082 (-0.181 to 0.018)	-0.057 (-0.144 to 0.030)	-0.087 (-0.183 to 0.008)	-0.083 (-0.172 to 0.005)	<i>-0.145</i> (-0.248 to -0.042)	<i>-0.146</i> (-0.246 to -0.047)	<i>-0.116</i> (-0.199 to -0.033)
Model II ²	-0.053 (-0.154 to 0.048)	-0.041 (-0.131 to 0.049)	-0.069 (-0.167 to 0.029)	-0.078 (-0.168 to 0.013)	<i>-0.135</i> (-0.242 to -0.029)	<i>-0.126</i> (-0.228 to -0.025)	<i>-0.122</i> (-0.206 to -0.037)
Venular fractal dimension							
Model I ¹	-0.022 (-0.122 to 0.079)	<i>-0.127</i> (-0.214 to -0.041)	-0.044 (-0.141 to 0.053)	<i>-0.093</i> (-0.182 to -0.004)	<i>-0.113</i> (-0.217 to -0.008)	<i>-0.146</i> (-0.246 to -0.046)	<i>-0.109</i> (-0.192 to -0.025)
Model II ²	-0.022 (-0.121 to 0.078)	<i>-0.126</i> (-0.213 to -0.040)	-0.047 (-0.143 to 0.049)	<i>-0.096</i> (-0.184 to -0.008)	<i>-0.113</i> (-0.218 to -0.008)	<i>-0.144</i> (-0.243 to -0.045)	<i>-0.110</i> (-0.193 to -0.026)

Values denote mean differences with 95% CIs in parentheses. Significant associations are set in italics. ¹ Adjusted for age, gender, race, educational level, mean arterial blood pressure, fasting blood glucose, total cholesterol and presence of stroke. ² Adjusted for age, gender, race, educational level, mean arterial blood pressure, fasting blood glucose, total cholesterol, presence of stroke and cerebral microbleeds, total WML volume and total brain volume/intracranial volume ratio.

the presence of any previous stroke on neuroimaging (higher, $p = 0.043$). Of the 268 eligible participants, 121 had NCI, 78 CIND-mild and 69 CIND-moderate. In general, participants with CIND-mild or CIND-moderate were more likely to be women, to be older, and to have a lower education and socioeconomic status, a higher diastolic blood pressure, prevalent stroke, a higher WML volume and a lower total brain volume/intracranial volume ratio (table 1).

In the multinomial age- and sex-adjusted logistic regression models, a reduced retinal arteriolar fractal dimension was associated with a higher risk of CIND-moderate, while a reduced venular fractal dimension was associated with a higher risk of CIND-mild and CIND-moderate. After further adjustment for other risk factors such as socioeconomic status, blood pressure, glucose, cholesterol levels and MRI markers, reduced fractal dimensions remained associated with both clinical outcomes of CIND-mild and CIND-moderate (table 3).

The age- and sex-adjusted linear regression models for global cognitive function as expressed by the composite VDB Z-scores in the entire cohort showed that both reduced arteriolar and venular fractal dimensions and a reduced arteriolar vessel tortuosity were associated with poorer cognitive performance (table 2). However, the association of cognitive impairment with arteriolar tortuosity was attenuated after additional adjustment for other risk factors and MRI markers (table 3).

As there were significant associations between fractal dimensions and global cognitive function, associations with specific cognitive domains were also investigated in this cohort. Reduced fractal dimensions were associated with lower scores in verbal memory, visuoconstruction and visuomotor speed (table 4).

Discussion

In this Chinese population, persons with a sparser vascular network in the retina were more likely to have poorer global cognitive performance and significant cognitive impairment, independent of traditional risk factors and MRI markers. In particular, they performed worse in specific cognitive domains of verbal memory, visuoconstruction and visuomotor speed.

Thus far, studies examining the relationship between retinal microvascular changes and cognitive dysfunction have mainly focused on clinically visible retinopathy signs. In the Atherosclerosis Risk in Communities (ARIC) study [20], classic retinopathy lesions were clearly associated with cognitive impairment. However, findings from other studies including the Los Angeles Latino Eye Study (LALES), the Cardiovascular Health Study (CHS), the Blue Mountain Eye Study (BMES) and the AGES-Reykjavik Study have been less clear [6, 21–23]. For example, in the BMES [23], these associations were only present among subjects with hypertension, whereas in the AGES-Reykjavik Study [6], retinopathy combined with the presence of cerebral microbleeds was associated with cognition. These discrepancies could be due not only to differences in the cognitive tests used, such as the MMSE or the AMT [12, 21, 23], but also to differences in the specific cognitive domains tested, such as psychomotor speed, executive function and verbal memory [20, 21]. Finally, retinopathy signs are considered relatively late indicators of vascular damage in the eye, and they indicate advanced stages of structural microvascular damage. Recent advances in digital retinal imaging have enabled us to quantify early changes in the retinal microvasculature.

In our present study, we focused on retinal vascular fractal dimensions. In addition to their potential to reflect earlier and more subtle changes before the appearance of overt signs, fractal dimensions in particular have the advantage of being parameters that do not vary with pulse cycles, such as vessel diameters. One previous study has shown that decreased fractal dimensions were related to cognitive dysfunction [12]. However, in that study, only a brief 10-point screening test (the AMT) was employed. In the current study, an extensive neuropsychological test battery was employed to assess a range of cognitive domains, allowing us not only to study individual domains but also to comprehensively stage our subjects into categories with increasing severity of impairment. Our data provide additional support that these changes in the retinal vascular network are associated with cognitive impairment. Furthermore, our findings that reduced arteriolar and venular fractal dimensions are associated with preclinical stages of dementia are in line with those of previous studies showing that these retinal parameters are linked not only to clinical outcomes such as acute ischemic stroke and dementia but also to markers of cerebral small vessel disease such as lacunar infarcts and cerebral microbleeds [8, 9, 24–26]. Pathophysiologically, a sparser network as reflected by a reduced fractal dimension is a consequence of retinal vessel rarefaction and collapse, which may lead to hypoxia in the retina [27]. Similarly, in the brain, destruction and occlusion of the small perforating vessels have been observed [28], suggesting that there may be parallel pathological mechanisms at work in the brain and the retina leading to microvascular changes. Taken together, these morphological changes in the retinal microvasculature suggest that subtle microvascular changes may already be present in the preclinical stages of dementia, further providing evidence for vascular disease as an important contributor to the development of cognitive impairment and dementia.

Some methodological issues need to be discussed. Since approximately half of the screening-positive subjects declined to take part in phase II of the study (cognitive assessment and neuroimaging phase), the eligible subjects who refused to participate may have had poorer cognitive function, and this may have led to an underestimation of the effect sizes [10]. Nevertheless, we still found a consistent association between retinal vascular network complexity and cognitive impairment, suggesting that the true association may be stronger.

The strengths of our study include the comprehensive and standardized assessment of cognitive ability over a range of domains and the quantitative evaluation of retinal photographs using standardized semiautomated protocols.

In conclusion, our study found that a sparser retinal microvascular network is associated with cognitive impairment and poorer performance on cognitive scores, independent of cardiovascular risk factors and MRI markers of cerebral small vessel disease. This provides additional evidence for the importance of microvascular pathology in the development of cognitive impairment.

Acknowledgements

The authors thank all the staff and participants of the EDIS study and the Singapore Epidemiology of Eye Disease Study for their important contributions. The EDIS study is supported by the National Medical Research Council, Singapore (NMRC/CG/NUHS/2010). M.K.I. received additional funding from the Singapore Ministry of Education Academic Research Fund (Tier 1 WBS-R-191-000-014-112), the Singapore Ministry of Health National Medical Research Council (NMRC/CSA/038/2013) and the National University Health System Clinician Scientist Program (NCSP).

Disclosure Statement

The authors have no conflicts of interest to disclose.

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