Preventive Medicine

Retinal Microvascular Abnormalities and Cognitive Impairment: Epidemiological Findings

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Abstract

Retinal microvascular abnormalities have been associated with age-related systemic processes, such as atherosclerosis, chronic inflammation, endothelial dysfunction, and other conditions. Current epidemiological studies suggested that retinal microvascular abnormalities may be associated with cognitive decline and thereby may provide a target for early detection and prevention of dementia. However, most of previous studies have been cross-sectional and provided only suggestive evidence. Future prospective studies with assessment of cognitive function on specific domains are required to further evaluate the role of retinal microvascular signs in predicting the development of aging-related cognitive decline and dementia.

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Key Words: *retinal vessel, cognitive function, epidemiology*

Introduction

With the increasing proportion of the elderly population, dementia has become a major public health concern. It was estimated that the people living with dementia will be 81.1 million by 2040.[1] Dementia is a chronic neurological degeneration. As people age, they would all experience normal age-related cognitive decline but some of them may deteriorate and develop dementia eventually if no interventions are implemented. Thus, early detection and identification of risk factors contributing to cognitive decline will provide an effective strategy for preventing dementia in the elderly.

Retinal microvascular abnormalities have been associated with age-related vascular processes, such as atherosclerosis, chronic inflammation, endothelial dysfunction, and other conditions. The retinal microvascular abnormalities may reflect systemic microvascular damages and can be examined with color fundus photography. With the computer-assisted imaging techniques, the retinal vascular signs can be graded and classified manually according to different abnormalities. Different studies had used different protocols for the retinal vascular grading. Among the published studies,[2-4] retinal vascular abnormalities have been classified into the following categories: 1) retinopathy such as microaneurysms, retinal hemorrhages, soft exudates, and hard exudates; 2) arteriovenous nicking; 3) focal arteriolar narrowing; and 4) generalized arteriolar narrowing, which can also be replaced by quantitative measurements of retinal vessel calibers. Previous studies have shown that retinal vessel signs were associated with vascular systemic process and cardiovascular disease mortality.[5-8] However, few studies have specifically investigated whether the retinal signs can be reliable markers for cognitive impairment and age-related dementia. This article aims to provide a comprehensive review of current population-based epidemiological studies on the association between retinal vessel signs and cognitive impairment.

Findings from Epidemiological Studies

In 2002, the Atherosclerosis Risk in Communities Study (ARIC) first published its findings on the association between retinal vessel signs and the cognitive function.[3] The ARIC study is a population-based study with examinations every 3 years starting from 1987. Retinal photographs were obtained from participants (age: 51-70 years) in visit 3. The retinal vessel abnormalities included: 1) retinopathy; 2) arteriovenous nicking; 3) focal arteriolar narrowing; and 4) generalized arteriolar narrowing. All participants at visits 2 and 4 had the following three cognitive function tests: the Delayed Word Recall Test (DWR), the Digit Symbol Subset of the Wechsler Adult Intelligence Scale-Revised (DSS), and the Word Fluency Test of the Multilingual Aphasia Examination (WFT). The mean scores of the cognitive functions tests from the two visits were used for analyses (n=7,526). The results showed that retinopathy was associated with lower cognitive test scores after controlling for education, diabetes, blood pressure, carotid Intima-Media Thickness (IMT), and other risk factors. The adjusted odds ratios (ORs) for persons with DWR scores 2 standard

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deviation (SD) or lower than the mean were 2.6 (95% confidence interval [CI], 1.3 to 2.9) for any retinopathy, 3.0 (95% CI, 1.8 to 5.0) for microaneurysms, 3.4 (95% CI, 2.0 to 5.8) for retinal hemorrhage, and 3.1 (95% CI, 1.5 to 6.2) for soft exudates. Similar results were found for other 2 cognitive tests, and in people with and without diabetes and hypertension.

In 2007, the Cardiovascular Health Study (CHS) reported the associations between retinal microvascular abnormalities and lower cognitive function and increased risk of dementia.[2] The CHS is a longitudinal population-based study beginning in 1989 at 4 field centers. During the 1997-98 clinic visits, digitized retinal photographs were obtained (n=4,249) and the retinal vessel abnormalities were evaluated. Cognitive function was assessed with Mini-Mental State Examination (MMSE) and DSS test at the same time of retinal photography (n=2,211). One year after retinal photography, a subset of participants was evaluated for the presence of dementia using a 3-stage system as part of a CHS cognition study. Persons with retinopathy had lower mean DSS scores but not MMSE than those without retinopathy (39 vs. 41, P=0.002) after adjusting for education, carotid IMT, hypertension, diabetes, and other risk factors. Retinopathy (OR, 2.1, 95% CI, 1.0 to 4.2), and focal arterial narrowing (OR, 3.0, 95% CI, 1.5 to 6.0) were associated with dementia after multiple adjustments among hypertensive participants.

The Blue Mountains Eye (BME) study is another study that provided similar evidence on the association between retinal vessel signs and cognitive impairment. In total, 1,988 participants aged 49 to 97 years were included in the analyses. The results showed that retinal venular dilation (larger retinal venular caliber) was associated cognitive impairment (MMSE score of 23 or less) after adjusting for education, blood pressure, diabetes, CVD, and other factors (OR=1.8, 95% CI, 1.0 to 3.2, P=0.03). Retinopathy was associated with cognitive impairment among hypertensive participants (OR=1.7, 95% CI, 1.0 to 3.2, P=0.05).

A study from UK on the retinal vascular network geometry provided similar evidence on the relations of retinal signs and cognitive function in older adults. A cohort of older participants aged 83-84 years (n=372) had their retinal fundus photographed; their parameters of the retinal vascular network geometry and retinal vessel calibers were measured from digitized retinal films. The participants had a battery of cognitive function tests including MMSE, Verbal Fluency test, the Moray House test, and logical memory test. They found that suboptimal retinal vascular network geometry was associated with low cognitive function: deviation of the median branching coefficient was significantly associated with general cognitive ability (p=0.02) and verbal fluency (p=0.01), and deviation of the angle at arteriolar bifurcations from optimality was associated with low logical memory (p=0.03) after adjusting for education, CVD, diabetes and other factors. However, the retinal vessel calibers were not associated with cognitive test performance.

As noted, all the above studies are cross-sectional analyses. Prospective data are very limited. Recently, the ARIC study published its results for a 14-year follow up period. Eight hundred and three participants (baseline age 58.4 years) had completed 4 visits of cognitive tests. This follow-up study found that participants with retinopathy showed a decline in cognitive function with an average decline in WFT of -1.64 words per decade (95% CI, -3.3 to -0.02) compared to no decline in those without retinopathy (0.06; 95% CI, -0.6 to 0.8) and a higher frequency of rapid decliners (those among the 10% with the greatest decline) on the DSS test.

Besides these studies, there were other clinic/hospital based studies, which investigated the retinal vascular abnormalities and cognitive function among diabetic patients.[9-11] These studies were usually of small sample size, and their conclusion may not be generalizable to the general population since diabetes itself is an important factor for cognitive impairment.

Epidemiologic Evidence: Retinal Microvascular Abnormalities and Cerebrovascular Damage

There is growing evidence that vascular factors play an important role in the development of dementia, Alzheimer's disease, and cognitive impairment.[12-14] However, the precise mechanisms remain poorly understood. Retinal vascular abnormalities, as a marker of systemic microvascular damage, may be associated with other macrovascular risk factors, such as hypertension,[15] therefore indicating a possible link with brain function changes. Also, retinal vascular signs may directly reflect the cerebrovascluar changes due to its homology to cerebrovasculature. Indeed, some studies have shown the association between retinal microvascular signs and cerebrovascular diseases. The ARIC study found that persons with cerebral white matter lesions (WMLs) detected by MRI were more likely to have retinal microvascular abnormalities and to have an increased risk of clinical stroke than people without WMLs.[16] The Rotterdam study found that retinal venular dilation was associated with insufficient blood supply to the brain[36] and predicted the progression of cerebral small vessel disease after 3.3 years of follow-up.[37]

Study Implication

As reviewed above, the current evidence from large population-based epidemiological studies seemed to be suggestive that retinal vessel signs may predict cognitive decline among older persons. However, most studies were of cross-sectional design and yielded inconsistent results. For example, the ARIC study (both cross-sectional and longitudinal analyses), the study from UK and the CHS study did not find the association of retinal vessel caliber to cognitive functions, while the BME study found that larger retinal venular caliber was associated with cognitive impairment. These discrepancies should be addressed in future studies.

It is also not clear which aspects of cognitive function are more likely to be influenced by the retinal abnormalities.

Previous studies only administered a few cognitive function tests, and some of them only applied MMSE, which is a test of general cognitive function but not sensitive to specific domains of cognitive function. Inconsistent results on these cognitive tests have been reported in these studies. For example, the BME study found the association with cognitive impairment measured with MMSE while the CHS study did not. The ARIC study found the association with all 3 cognition tests at baseline, while in the longitudinal study, the association was found with two tests which reflect executive function (WFT) and psychomotor speed (DSS), but not memory function (DWR).

Conclusion

In summary, due to the homology between retina and the brain, retinal vessel signs have been suggested to reflect the similar pathological change of cerebral vessels and may thus be a marker of cognitive degeneration related to age-related brain dysfunction. The measurements of retinal microvascular abnormalities are non-invasive and much more cost efficient comparing to the other costly methods such as MRI to detect early cerebrovascular damages. Thus, it may provide a strategy for early detection and prevention of dementia. Current evidence, although scarce and inconclusive, appears to support the association between retinal abnormalities and cognitive impairment. However, further studies, especially longitudinal assessments using more sensitive tests covering different domains of cognitive function are required to elucidate the predictive values of retinal microvascular signs in the degeneration of cognitive function in adults.

References

1. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. Lancet. 2005; 366(9503):2112-2117.
2. Baker ML, Marino Larsen EK, Kuller LH, et al. Retinal microvascular signs, cognitive function, and dementia in older persons: the Cardiovascular Health Study. Stroke. 2007;38(7):2041-2047.
3. Wong TY, Klein R, Sharrett AR, et al. Retinal microvascular abnormalities and cognitive impairment in middle-aged persons: the Atherosclerosis Risk in Communities Study. Stroke. 2002;33(6):1487-1492.
4. Liew G, Mitchell P, Wong TY, et al. Retinal microvascular signs and cognitive impairment. J Am Geriatr Soc. 2009; 57(10):1892-1896.
5. Ikram MK, de Jong FJ, Bos MJ, et al. Retinal vessel diameters and risk of stroke: the Rotterdam Study. Neurology. 2006; 66(9):1339-1343.
6. van Hecke MV, Dekker JM, Nijpels G, et al. Are retinal microvascular abnormalities associated with large artery endothelial dysfunction and intima-media thickness? The Hoorn Study. Clin Sci (Lond). 2006; 110(5):597-604.
7. Wang JJ, Liew G, Klein R, et al. Retinal vessel diameter and cardiovascular mortality: pooled data analysis from two older populations. Eur Heart J. 2007;28(16):1984-1992.
8. Wong TY, Klein R, Couper DJ, et al. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. Lancet. 2001;358(9288):1134-1140.
9. Ryan CM, Geckle MO, Orchard TJ. Cognitive efficiency declines over time in adults with Type 1 diabetes: effects of micro- and macrovascular complications. Diabetologia. 2003;46(7):940-948.
10. Kadoi Y, Saito S, Fujita N, Goto F. Risk factors for cognitive dysfunction after coronary artery bypass graft surgery in patients with type 2 diabetes. J Thorac Cardiovasc Surg. 2005;129(3):576-583.
11. Ferguson SC, Blane A, Perros P, et al. Cognitive ability and brain structure in type 1 diabetes: relation to microangiopathy and preceding severe hypoglycemia. Diabetes. 2003;52(1):149-156.
12. Viswanathan A, Rocca WA, Tzourio C. Vascular risk factors and dementia: how to move forward? Neurology. 2009;72(4):368-374.
13. Stampfer MJ. Cardiovascular disease and Alzheimer's disease: common links. J Intern Med. 2006;260(3):211-223.
14. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. 2005;64(2):277-281.
15. Wong TY, McIntosh R. Systemic associations of retinal microvascular signs: a review of recent population-based studies. Ophthalmic Physiol Opt. 2005;25(3):195-204.
16. Wong TY, Klein R, Sharrett AR, et al. Cerebral white matter lesions, retinopathy, and incident clinical stroke. JAMA. 2002;288(1):67-74.