ELSEVIER

Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 1 (2015) 229-235

Alzheimer's & Dementia

Retinal microvascular network attenuation in Alzheimer's disease

Michael A. Williams[a,1], Amy J. McGowan[b,1], Chris R. Cardwell[b], Carol Y. Cheung[c,d], David Craig[e], Peter Passmore[b], Giuliana Silvestri[f], Alexander P. Maxwell[b], Gareth J. McKay[b,*]

[a]*Centre for Medical Education, Queen's University Belfast, Belfast, UK*
[b]*Centre for Public Health, Queen's University Belfast, Belfast, UK*
[c]*Singapore Eye Research Institute, Singapore National Eye Centre, Singapore, Singapore*
[d]*Ophthalmology and Visual Sciences Academic Clinical Programme, Duke-NUS Graduate Medical School, National University of Singapore, Singapore, Singapore*
[e]*Southern Health and Social Care Trust, Craigavon Hospital, Craigavon, UK*
[f]*Centre for Experimental Medicine, Queen's University Belfast, Belfast, UK*

Abstract

Introduction: Cerebral small-vessel disease has been implicated in the development of Alzheimer's disease (AD). The retinal microvasculature enables the noninvasive visualization and evaluation of the systemic microcirculation. We evaluated retinal microvascular parameters in a case-control study of AD patients and cognitively normal controls.

Methods: Retinal images were computationally analyzed and quantitative retinal parameters (caliber, fractal dimension, tortuosity, and bifurcation) measured. Regression models were used to compute odds ratios (OR) and confidence intervals (CI) for AD with adjustment for confounders.

Results: Retinal images were available in 213 AD participants and 294 cognitively normal controls. Persons with lower venular fractal dimension (OR per standard deviation [SD] increase, 0.77 [CI: 0.62–0.97]) and lower arteriolar tortuosity (OR per SD increase, 0.78 [CI: 0.63–0.97]) were more likely to have AD after appropriate adjustment.

Discussion: Patients with AD have a sparser retinal microvascular network and retinal microvascular variation may represent similar pathophysiological events within the cerebral microvasculature of patients with AD.

Keywords: Retina; Retinal vasculature; Alzheimer's disease; Microcirculation; Small-vessel disease

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia and a major increasing public health concern [1]. The gold-standard for the diagnosis of AD is the identification on post-mortem of amyloid-beta and neurofibrillary tangles [2]. It is not clear how these pathologic features result in the clinical manifestations of AD. Although AD is described as a neurodegenerative condition, it is argued that the failure of the "neurovascular unit" underlies the condition [3]. Both structural and functional cerebral vascular changes have been described in vivo and in animal models of AD [4].

The cerebral and retinal vasculature share similar embryologic origins, anatomic features, physiological properties, and regulatory mechanisms [5], and it is perhaps unsurprising that retinal changes have also been observed in AD [6–8]. Amyloid-beta has been identified in the retinal

Financial support: Supported by the Medical Research Council United Kingdom Grant MR/K003364/1 and Diabetes United Kingdom Grant 11/0004400. M.A. Williams was supported in this work by a Royal College of Physicians/Dunhill Medical Trust Clinical Research Fellowship, and an Alzheimer's Research Trust Grant. A.J. McGowan was supported by a Diabetes UK PhD Studentship Award.

[1]Both authors have contributed equally to this work.

*Corresponding author. Tel.: +44-(0)2890635232; Fax: +44-(0)2890235900.

E-mail address: g.j.mckay@qub.ac.uk

http://dx.doi.org/10.1016/j.dadm.2015.04.001

and choroidal microvasculature from mouse models of AD [9]. Berisha and colleagues reported a significant difference in the retinal venous blood column diameter between nine patients with mild to moderate AD and eight controls ($P = .01$), with AD cases having narrower veins, and a reduction in blood flow ($P = .002$) [10]. Further support arose from a much larger study, in which narrower retinal venules and a sparser and more tortuous vessel network was observed in 136 patients with AD compared with 290 matched cognitively normal controls [6].

There is now greater reliability in the assessment of a wider range of retinal parameters beyond vessel caliber, including fractal dimension, tortuosity, and vessel bifurcation which provide a global indication of the "optimality" and "efficiency" of blood distribution throughout the retinal network [11–14]. These retinal features have been postulated to reflect the integrity of the cerebral microcirculation and have been associated with stroke, implicating early microvascular network abnormalities in the pathophysiology of these conditions [14–16]. Previous studies have shown association between retinal vascular changes and AD, although the effects observed have not always been either consistent or adjusted for the potential confounding of medication use. Retinal vascular changes identified in association with AD may offer value both for understanding the disease etiology and perhaps aid the early, noninvasive diagnosis of this disease [17].

The aim of this study was to compare a spectrum of retinal vascular parameters in a large sample consisting of two cohorts, one of patients with AD and another of cognitively normal controls. We hypothesize that changes within the retinal microvascular network may reflect alterations within the cerebral microcirculation of those with AD.

2. Methods

2.1. Study population

This was a prevalent case-control study comparing cases with AD to cognitively normal controls. All recruitment and testing was performed by one investigator (MW) and has been described elsewhere [18]. An opportunistic recruitment strategy was used. Potential cases with AD were identified in a nonsystematic fashion as they appeared in clinic or files from the population of those with a diagnosis of AD, made by a senior clinician using the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria [19], attending a hospital memory clinic. Those with any other type of dementia were not included, including vascular or mixed dementia. Controls were recruited in several ways. First, carers of patients attending any out-patient clinic in the study hospital were approached as opportunities arose. Second, a university press release generated interest. Third, controls asked friends to participate. Finally, a series of talks given to AD patient support groups in the region led to volunteers. Exclusion criteria for controls were age under 65 years, Mini-Mental State Examination (MMSE) score less than 26 of 30 and unmasking of any ophthalmic history before recruitment. Testing consisted of a questionnaire, blood pressure measurement, and drawing of a blood sample to identify any confounding factors. Ethical and clinical governance approval was granted before the commencement of the study. The study followed the tenets of the Declaration of Helsinki.

2.2. Retinal photography and quantitative measurements of retinal microvasculature

Retinal photography was performed through the dilated pupil using a 500 Canon CR-DGi digital camera, after the instillation of one drop of 1% tropicamide in all participants. A semiautomated computer-assisted program (Singapore I Vessel Assessment [SIVA], software version 3.0) was used to quantitatively measure the retinal vascular parameters from the photographs. SIVA automatically identifies the optic disc, places a grid with reference to the center of the optic disc, identifies vessel type, and calculates retinal vascular parameters. A single trained grader (AMG), blinded to participant characteristics, performed SIVA automated measurement and manual intervention if necessary, according to a standardized protocol [20]. The measured area was standardized and defined within the region between 0.5 and 2.0 disc diameters away from the disc margin, and all visible vessels coursing through the specified zone were measured (Fig. 1).

2.3. Retinal vascular caliber

Retinal vascular caliber was measured using the SIVA program following the standardized protocol used in the Atherosclerosis Risk in Communities study [21]. The retinal arteriolar and venular calibers were summarized as central retinal arterial equivalent (CRAE) and central retinal venular equivalent (CRVE), respectively, according to the revised Knudtson-Parr-Hubbard formula [22]. The reproducibility of retinal vascular measurements was high, with intragrader reliability assessed in 200 randomly selected retinal photographs and an intraclass correlation coefficient (95% confidence interval [CI]) calculated as 0.98 (CI: 0.97–0.98) for CRAE and 0.99 (CI: 0.99–0.99) for CRVE, respectively. A high correlation between the right and left eyes in retinal vascular measurements has been reported elsewhere [23]. Data from the right eye were used and when unavailable was replaced by left eye data.

2.4. Retinal vascular fractal dimension

Total, arteriolar, and venular fractal dimensions were determined from a skeletonized line tracing using the box