REVIEW

Retinal pathology as biomarker for cognitive impairment and Alzheimer’s disease

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ABSTRACT
Alzheimer’s disease (AD) is the most common cause of dementia. Furthermore, over the last few decades, there has been a shift towards identifying earlier stages of AD, which include mild cognitive impairment (MCI). Improved methods of screening and early detection are essential to identify cognitively normal individuals who have a high risk of developing MCI and AD, so that interventions can be developed to delay the progression of specific disease-related pathologies. Thus far, novel biomarkers that have been examined include structural and functional neuroimaging as well as biochemical analysis of cerebrospinal fluid. However, in spite of these efforts, there is still an urgent need for unravelling additional novel biomarkers for AD and MCI. As the retina shares many features with the brain, including embryological origin, anatomical (such as microvascular bed) and physiological characteristics (such as blood-tissue barrier), it has been suggested that the retina may provide an easily accessible and non-invasive way of examining pathology in the brain. While most AD-related pathology occurs in the brain, the disease has also been reported to affect different regions of the retina, including the macular region and optic disc. Studies have suggested that retinal pathology, such as deposits in the macular region, decreased retinal nerve fibre thickness, and optic disc cupping and retinal microvascular abnormalities may be related to AD and cognitive impairment. This article presents a review of current literature on retinal involvement in AD and MCI.

INTRODUCTION
As a result of rapid demographic ageing, the burden from common age-related brain diseases, such as dementia, is expected to rise exponentially.1,2 Currently, the global prevalence of dementia is estimated to be as high as 24 million, and is predicted to double every 2 decades.1 In terms of costs, in the USA alone, dementia is associated with an estimated healthcare cost of US$ 172 billion per year.1 Alzheimer’s disease (AD) is the leading cause of dementia, and is characterised by a progressive decline in cognitive function, which typically begins with deterioration in memory. Among regional populations of individuals aged >60 years, the prevalence of AD ranges from 6.4% in North America and Western Europe to 4.9% in Latin America, and 4.0% in China. In contrast, for mild cognitive impairment (MCI), which is considered a transitional stage to early AD, a much wider range has been reported (3–42%).1,2

Although substantial progress has been made over the past few decades in understanding AD, our ability to translate this into clinical benefits remains limited, as demonstrated by the diagnostic uncertainty inherent to the present criteria to diagnose AD, and the fact that currently only symptomatic treatments are available for clinically diagnosed AD.1,3 It can be argued that improved methods of screening and early detection are essential to identify cognitively normal individuals who have a high risk of developing MCI and AD, so that interventions can be developed to delay the progression of specific disease-related pathologies. Over the last few decades, there have been major advances in unravelling novel biomarkers for AD and MCI using state-of-the-art neuroimaging and biochemical analysis of the cerebrospinal fluid (CSF). Although clinical symptoms of dementia become manifest late in the course of the disease, it has been shown that the underlying subclinical pathology (such as cerebral atrophy and white-matter lesion on MRI, changes in Aβ-42 in the CSF) is widespread in the population and may be present many years before symptoms of cognitive impairment.1,2 However, in spite of these efforts, there is currently no definitive ante-mortem diagnosis for AD, and therefore, there is still an urgent need for unravelling novel biomarkers for AD and MCI. Over the last decade, advances in retinal imaging have opened new possibilities of using the retina as a template to examine pathology in the brain, and thereby elucidate novel biomarkers for AD and MCI. In this review, we provide a comprehensive update on the role the retina may play in providing novel biomarkers for AD and MCI.

METHODOLOGY
References were identified through PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) with the search terms: ‘retina AND dementia’ (280 references found), ‘retina AND Alzheimer’s disease’ (258), ‘retinal AND Alzheimer disease’ (469), ‘cognitive impairment AND retina’ (47) between January 1970 and February 2012. The references from identified articles and the authors’ own files were also searched for relevant publications. Only papers published in English were reviewed. The final list of 68 references was chosen on the basis of relevance to the topic covered in this article.

BIOMARKERS FOR ALZHEIMER’S DISEASE
Currently, a diagnosis of ‘probable’ AD is made using the NINCDS-ADRDA criteria, and is only