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Imaging Retinal Amyloid – The Virtual Brain Biopsy

Coad Thomas Dow*

McPherson Eye Research Institute University of Wisconsin-Madison and Chippewa Valley Eye Clinic, USA

Abstract

Alzheimer's Disease (AD) is mostly regarded as Alzheimer's disease dementia. AD is diagnosed with certitude at autopsy or via brain biopsy. However, it is now known that the AD pathological abnormalities, detected in vivo by biological markers, precede the clinical symptoms by years or even decades. The uniform lack of success in treating AD may be due to the fact that therapeutic intervention is begun too late in the course of the disease. The earliest recognizable pathological event in AD is aggregated cerebral amyloid-β deposition; this pathology may be present 20 years before the onset of dementia. A newly developed retinal camera visualizes amyloid in the retina and, through computer analysis, quantifies it yielding a number: the retinal amyloid index. The retina is an extension of the brain and early studies show that the amyloid deposition in the retinal correlates with cerebral amyloid deposition. This article introduces this imaging technology and suggests a role for early detection of the pathology associated with AD. Moreover, the utility of this technology in monitoring interventional trials is suggested. If the sensitivity and specificity of this imaging of retinal amyloid is successful enough to be embraced by the research community, it may ultimately be considered a "virtual brain biopsy.

Introduction

Alzheimer's disease (AD) is the most common cause of dementia with a worldwide prevalence of about 25 million in 2010 and is expected to double by 2030 because of increased life expectancy [1]. The traditional diagnosis of AD connotes "Alzheimer's disease dementia" – when the disease is in the late stage [2]. More recently, the clinical disease stages of AD have been divided into three phases. First is a pre-symptomatic phase in which individuals are cognitively normal but some have AD pathological changes. Labeling these individuals as having pre-symptomatic AD is conjecture rather than fact, as some of these individuals will die without ever expressing clinical symptoms [3-5]. The hypothetical assumption is that an asymptomatic individual with pathological changes that are indicative of AD would ultimately have become symptomatic if he or she lived long enough. Second is a prodromal phase of AD, commonly referred to as Mild Cognitive Impairment (MCI) [6], which is characterized by the onset of the earliest cognitive symptoms (typically deficits in episodic memory) that do not meet the criteria for dementia. The severity of cognitive impairment in the MCI phase of AD varies from the earliest appearance of memory dysfunction to more widespread dysfunction in other cognitive domains. The final phase in the evolution of AD is dementia is impairment that is severe and produces loss of function. Diagnostic certitude in AD in only attained at autopsy or via a brain biopsy.

The earliest recognizable pathological event in AD is cerebral amyloid-β aggregation [7]. A widely accepted assumption is that AD begins with abnormal processing of Amyloid Precursor Protein (APP), which then leads to excess production or reduced clearance of β-amyloid (Aβ) in the cortex [8]. This pathology may be present up to 20 years before the onset of dementia [9,10]. AD is a slowly progressing disease with pathological findings that can be detected in vivo with biological markers. The recognized biomarkers for AD include neuroimaging tests for characteristic neurodegeneration and analysis of Cerebral Spinal Fluid (CSF) to detect amyloid and related tau-protein.

An example of biomarker use in an at-risk population is the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) trial (http"//a4study.org) [11,12]. This large study selects cognitively normal participants who are amyloid positive on PET scan for randomization for intervention with an antibody that targets amyloid or with placebo.

Although each of the accepted biomarkers have a current place in evaluating patients for AD, suffice it to say that better, more sensitive and specific, less costly, less invasive biomarkers are needed. Moreover, it has been shown that there is a large variability in measurements of the core AD biomarkers between clinical centers and laboratories [13].

Retinal Amyloid Imaging

Researchers at Cedars-Sinai in Los Angeles have shown that, with special attention, aggregated amyloid in the retina could be directly visualized. Tumeric, a natural product found in the spice curry, when ingested both binds to amyloid and naturally fluoresces; properties that are exploited to visualize amyloid in the retina with a specially adapted retinal camera. With this they studied and reported that amyloid plaques are identified and "scored" with noninvasive, in vivo optical testing (Figure 1). The test images are used to generate a number: the retinal amyloid index. Understanding that the retina is a direct extension of the brain, they showed that the retinal amyloid correlates with the similar pathology in the brain [14,15]. The information was featured on cable television [16].

Would I Want to Know?

While assessing retinal amyloid does not carry the costs and risks of current AD biomarker testing, a legitimate question is whether or not an individual would want to know that they are at risk for AD albeit by a simple non-invasive test. The truth of the matter is that we all, with age, are depositing amyloid in our brains [17]. Disclosing both PET scan results as well as genetic risk due to APOE carrier status has been

***Corresponding author:** Coad Thomas Dow, McPherson Eye Research Institute University of Wisconsin-Madison and Chippewa Valley Eye Clinic, 2715 Damon Street Eau Claire, Wisconsin 54701 USA. Tel: 715 834 8471; E-mail: ctdow@me.com

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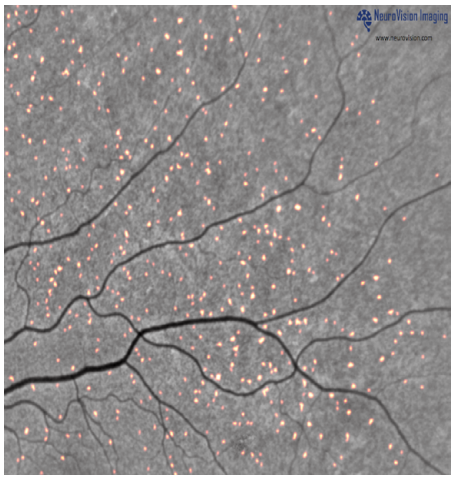

Figure 1: Retinal amyloid detected via fluorescence with a specially adapted retinal Camera-courtesy of Neuro Vision Imaging.

addressed; in these studies disclosure did not make an emotional impact on those found to be at higher risk. Subjects identified with higher risk, however, did make positive changes in their lifestyles. Indeed, the discovery and validation of a broad spectrum of interventions, including pharmacologic and lifestyle "treatments" continue to be an urgent global public health objective [18-20]. The first several treatments for AD have failed to demonstrate efficacy perhaps because they were started too late in the disease process when AD pathology is irreversible. Identification of the preclinical stage would seem to offer an opportunity for successful treatment [21].

Discussion

The use of one or more of the established AD biomarkers (CSF tau and Aβ and/or amyloid PET), to support the diagnosis of AD prior to inclusion in clinical treatment trials is becoming close to standard practice [22]. The pathology of AD: amyloid protein aggregation, synaptic dysfunction, inflammation and brain atrophy all can occur independent of each other and these changes are neither linear nor parallel [7,23,24]. These are confounding issues as they relate to the treatment of AD. However, the opportunity to identify the preclinical AD state will likely be critical to effectively evaluate potential disease-modifying agents. If retinal amyloid testing achieves widespread approval in the research community, it will likely become a sole biomarker for preclinical AD used for outcome analysis of studied treatments. Preclinical detection, course trajectory and response to lifestyle and/or pharmacologic intervention could all be measured and monitored with the Retinal Amyloid Index. If this comes to pass, the testing faithfully reflecting AD brain pathology and demonstrating disease modification, imaging retinal amyloid will become a "virtual brain biopsy."

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