Commentary: Eye as a window to the brain

The risk of developing Alzheimer's disease (AD) with age doubles every 5.9 years from 3.1 per 1000 persons age 60–64 years to 175 persons per 1000 at age 95+ years, making age the strongest risk factor for AD.[1]

The eye, specifically the retina, shares the same embryological origin and vasculature as the central nervous system and is its only extension outside the skull.[2] Hence, it allows for noninvasive visualization of neural integrity. The inner blood–retinal barrier and blood–brain barrier are quite similar and so are the aqueous humour and cerebrospinal fluid. The eye and the brain may share common disease-specific pathological mechanisms, as in stroke and multiple sclerosis and these have been used for the prediction, diagnosis, and prognosis of these diseases.[2]

However, the process of retinal degeneration in relation to brain degeneration in AD is not fully understood. Retinal degeneration could be a result of brain degeneration and therefore occurs after neurodegeneration or could be an unrelated phenomenon that can precede, occur simultaneously to, or not occur in the presence of brain degeneration.[3] Measures of cortical degeneration would need to be evaluated as part of longitudinal studies in preclinical AD to determine this association with certainty because there is insufficient evidence to date to support any of these postulations.[3]

Lim *et al*. state that a challenge in using the macular ganglion cell complex (GCC) or retinal nerve fiber layer (RNFL) as biomarkers is its specificity, which is prone to confounds introduced by aging and other coexisting pathologies such as glaucoma.[1] Age-related changes are thought to be much more generalized, whereas there is some evidence for more sectoral losses in diseases such as AD and glaucoma. Whether AD and glaucoma exhibit mutually exclusive patterns of loss remains to be seen. The availability of *wide-field spectral domain optical coherence tomography (OCT)* (Heidelberg Engineering, 2016) has increased our capacity to topographically map GCC and RNFL changes.[1]

Fundus cameras and OCT are common place in eye clinics. Emerging technologies such as *OCT angiography, enhanced depth imaging OCT (EDI-OCT), and polarization sensitive OCT (PS-OCT)* will contribute to the increase in sensitivity and diagnostic capacity for AD.[1] Ophthalmologists may play a larger role in the provision of care for patients with AD. A range of neurological diseases including AD, Parkinson's disease (PD), and other dementias may stand to benefit from ocular biomarker technology, as a means to improve understanding, monitoring, and to help facilitate discovery of therapies.[1]

The clinical diagnosis of AD and PD is a challenging task, since there are no definite *in vivo* biomarkers. Nunes *et al*. highlighted that *texture analysis*, which encompasses a wide range of methods that allow for the characterization of the underlying image patterns, is a promising tool in the study of biomarkers for neurodegenerative diseases.[4]

Texture conveys information on the regular or irregular distribution of image intensity and the structural arrangement of the different retinal layers and how they differ between the health, AD, and PD conditions.[4] Texture analysis of OCT data may represent a simple, inexpensive, and noninvasive method of directly assessing neurodegeneration. SVM, a *supervised machine learning method*, may aid in the concomitant clinical diagnosis of AD and PD, even in the absence of univariate differences on average thickness.[4]

In addition, functional change in the electrical response of specific brain regions may be early markers in AD. This might arise as neuronal changes signaling damage which

may precede the conversion to clinical disease. Researchers have measured *visually evoked potentials*, with a reversing checkerboard stimulus producing P1 and N1 components that are substantially reduced in patients with advanced AD.[1] This is associated with losses in the retinal GCC-derived *pattern electroretinogram*. Studies using *multifocal electroretinogram* have shown changes in the macular region in early AD patients.[1]

The current article comprehensively covers various ocular biomarkers that could play a role in the early diagnosis of AD.[5]

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