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Imaging retina to study dementia and stroke

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ABSTRACT

With increase in life expectancy, the number of persons suffering from common age-related brain diseases, including neurodegenerative (e.g., dementia) and cerebrovascular (e.g., stroke) disease is expected to rise substantially. As current neuro-imaging modalities such as magnetic resonance imaging may not be able to detect subtle subclinical changes (resolution <100–500 μm) in dementia and stroke, there is an urgent need for other complementary techniques to probe the pathophysiology of these diseases. The retina - due to its anatomical, embryological and physiological similarities with the brain - offers a unique and accessible "window" to study correlates and consequences of subclinical pathology in the brain. Retinal components such as the microvasculature and retinal ganglion cell axons can now be visualized non-invasively using different retinal imaging techniques e.g., ocular fundus photography and optical coherence tomography. Advances in retinal imaging may provide new and potentially important insights into cerebrovascular neurodegenerative processes in addition to what is currently possible with neuro-imaging. In this review, we present an overview of the current literature on the application of retinal imaging in the study of dementia and stroke. We discuss clinical implications of these studies, novel state-of-the-art retinal imaging techniques and future directions aimed at evaluating whether retinal imaging can be an additional investigation tool in the study of dementia and stroke.

Contents

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1. Introduction

With increase in life expectancy, the number of persons suffering from common age-related brain diseases, including neurodegenerative (e.g., dementia) and cerebrovascular (e.g., stroke) disease is expected to rise substantially (Cotter, 2007; Larson and Langa, 2008). In Western countries, one in four persons above the age of 55 years will develop dementia, and one in five will suffer a stroke (Donnan et al., 2008; Fox et al., 2001; Rimmer et al., 2005). Globally, these brain diseases constitute a major health and societal burden for patients and their families. As therapeutic options are limited, effective preventive strategies and methods for early diagnosis are needed. While clinical symptoms for both dementia and stroke manifest late in the disease course, the underlying subclinical pathological processes (e.g., cerebral atrophy, white matter lesions and microvascular diseases) occur much earlier and in fact are highly prevalent in the older population years before the onset of clinical disease (Ferri et al., 2005; Sahadevan et al., 2008; Venketasubramanian et al., 2005).

Non-invasive neuroimaging tools such as magnetic resonance imaging (MRI), are the most widely used modality to study subclinical pathology in dementia and stroke. Studies show subclinical structural brain changes seen on MRI (e.g. periventricular and subcortical white matter lesions, lacunar infarcts, microbleeds, atrophy) are related to future risk of dementia and stroke (Kantarci, 2005; Smith et al., 2003; Vermeer et al., 2003). While MRI measures are considered as good candidates, they may not be useful at the early stages of the pathological process and still cannot determine many of the mechanisms that underlie the subclinical brain changes due to limitations in spatial resolution to detect subtle degenerative and microvascular changes of less than 500 μm (Pantoni and Garcia, 1997). Furthermore, although other biomarkers, including the detection of increased amyloid and tau deposition by positron emission tomography (PET) imaging and assays for amyloid and tau in cerebrospinal fluid, have been developed in dementia research in recent years, the availability and acceptability of these examinations are limited to highly specialized clinics with cost-intensive equipment, and are unlikely to be widely available. Additional tools to study subclinical pathology and biomarkers of dementia and stroke are therefore needed.

The retina shares similar embryological origin, anatomical features and physiological properties with the brain and hence offers a unique and accessible “window” to study the correlates and consequences of subclinical pathology in both dementia and stroke (Cheung et al., 2014b; London et al., 2013; Patton et al., 2005). The retinal microvasculature can now be visualized, quantified and monitored non-invasively using ocular fundus photography and computer software image analysis. In addition, retinal ganglion cell (RGC) axons, the ocular extension of the central nervous system (CNS), can also be measured and quantified using optical coherence tomography (OCT). Fig. 1 illustrates the retina as a model to study cerebral microvascular and neuronal damage using retinal imaging. These retinal imaging tools offer unique information on the status of the cerebral microvasculature and neuronal structure that is distinct from brain imaging measures, suggesting that retinal imaging provides a complementary approach to study the pathophysiology of dementia and stroke, and may support a given diagnosis or prognosis (Cheung et al., 2014b, 2015a; Heringa et al., 2013; Ikram et al., 2012; MacGillivray et al., 2014; Patton et al., 2005, 2006).

In this review, we summarize recent findings on the application of retinal imaging as a tool to study the pathophysiology of both neurodegenerative (dementia) and cerebrovascular (stroke) diseases. We will finally discuss the clinical implications of these findings and future research directions.

2. The retina as a model to study cerebral microvascular and neuronal damage

During embryonic development, the retina and optic nerve develop as a direct extension of the diencephalon. In terms of the microvasculature, the retinal arterioles and venules, measuring 100–300 μm in diameter, share similar features with cerebral small blood vessels including end arterioles without anastomoses, barrier function, auto-regulation and relatively low-flow and high-oxygen-extraction systems, which allow a unique perspective on the cerebral microvasculature, in particular new insights into the microvascular etiology (versus macrovascular etiology) of diseases (Cheung et al., 2014b, 2015a; Ikram et al., 2012; London et al., 2013; Patton et al., 2005, 2006). Moreover, the retina is composed of layers of specialized neurons that are interconnected through synapses. RGCs - displaying typical properties of CNS neurons and comprising a cell body, dendrites and an axon - are neurons located in the ganglion cell layer in the retina that receive visual information from photoreceptors via various intermediate neuronal cells in the retina, including the bipolar, amacrine, and horizontal cells (Wassle, 2004). Visual information is passed along the axons of RGCs, which are myelinated as they leave the eyes, forming the optic nerve. The optic nerves converge at the optic chiasm before partial decussation and continuing as the optic tracts to terminate at the lateral geniculate nucleus, where visual information is relayed to the visual cortex in the occipital lobe, providing the connection between the eye and the CNS (Dowling, 2012; Wassle, 2004). Given this strong connection, it has been suggested that neurodegenerative processes in the brain may also lead to similar changes in RGCs and optic nerve (Ho et al., 2012; London et al., 2013).

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