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Review Article

Alzheimer's disease in the human eye. Clinical tests that identify ocular and visual information processing deficit as biomarkers

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Abstract Alzheimer's disease (AD) is the most common form of dementia with progressive deterioration of memory and cognition. Complaints related to vision are common among AD patients. Several changes in the retina, lens, and in the vasculature have been noted in the AD eye that may be the cause of visual symptoms experienced by the AD patient. Anatomical changes have been detected within the eye before signs of cognitive impairment and memory loss are apparent. Unlike the brain, the eye is a unique organ that can be visualized noninvasively at the cellular level because of its transparent nature, which allows for inexpensive testing of biomarkers in a clinical setting. In this review, we have searched for candidate biomarkers that could enable diagnosis of AD, covering ocular neurodegeneration associated with functional tests. We explore the evidence that suggests that inexpensive, noninvasive clinical tests could be used to detect AD ocular biomarkers.

Keywords: Retina; Retinal degeneration; Glaucoma; Ganglion cells; Amyloid

1. Introduction

Alzheimer's disease (AD) is a debilitating illness, estimated to affect 36 million people worldwide as of 2010 [1]. The signs and symptoms of AD can be very heterogeneous because different areas of the brain are damaged to varying extent. There is presently no cure for the disease, although treatments aiming at relieving symptoms of the disease and techniques that identify biomarkers have emerged [2]. Despite having a greater understanding of the underlying pathophysiology of the disease, current diagnostic tests rely on the use of invasive, expensive, or cognitively demanding tests for AD patients. The best efforts to find effective diagnostic techniques and treatments rely on the understanding of new emerging biomarkers for AD and access to economical diagnostic techniques [2]. The pathology of AD leads to significant cell death, particularly in the cerebral cortex and certain subcortical regions. The resultant neuronal death results in tissue loss in the parietal lobe, temporal lobe, frontal cortex, and certain areas of the cingulate gyrus [3], affecting bodily physiological functions in addition to cognition. Therefore, in early stages of the disease, noncognitive pathways may be affected, leading to prospective early biomarkers of the disease. In addition, research suggests that many AD-related changes may take place within the eye, including retinal changes such as nerve fiber layer thinning and associated optic nerve head (ONH) cupping and changes within the lens and blood vessels [3–6]. This review examines the visual changes that occur in AD and evaluates the potential role of ophthalmologic and optometric noninvasive and easy-to-conduct tests in the detection of biomarkers of neuronal injury for AD.

2. Molecular evidence of AD affecting the visual pathway

2.1. Protein deposition in the retina

The eyes are sensory extensions of the brain from as early as the fourth week of gestation. Once the retinal

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nerve fiber layer (RNFL) and the optic nerve are formed, they are the most relevant in acting as the window to the brain because their axons synapse directly with several brain regions. Several reports suggest that biomarkers of AD may be present within the optic nerve and retina at the molecular level [7,8]. In the AD brain, amyloid-β (Aβ) and hyperphosphorylated tau are deposited, forming insoluble aggregates termed senile plaques (SPs) and neurofibrillary tangles (NFTs), respectively, which are believed to lead to neurotoxic damage and neuronal death in brain areas including the visual cortex [9]. Likewise, SPs and NFTs are present in the retina of AD patients and may contribute to retinal ganglion cell (RGC) death and consequent thinning the RNFL and morphological changes in the optic nerve [4,10,11]. Recent studies using transgenic animal models for AD have shown altered amyloid precursor protein (APP) processing and fibrillar Aβ deposition in all six layers of the neuroretina [12] and retinal vasculature [12,13], with the extent proportional to the increasing age of the animals. Because there is SP and NFT deposition in the visual cortex and neuroretina, it is difficult to gauge whether the visual dysfunction observed in AD patients is present early in the disease or whether it is a consequence of the underlying disease process. However, Koronyo-Kamaoui et al [8] have demonstrated in a mouse model of AD that retinal plaques detected ex vivo after the administration of curcumin, a plaque-labeling fluorochrome yet to be studied in clinical trials, preceded plaque deposition in the brain. This is an important finding because it suggests that the Aβ deposition seen among ganglion cells [13] could be an early related sign of AD development.

It has more recently been suggested that soluble oligomers of Aβ accumulate in synapses, triggering impairments in synaptic plasticity and memory before fibrillar Aβ deposition and neurodegeneration [14,15]. Soluble Aβ oligomers have also been detected in the retina [16]. Extensive evidence indicates that Aβ oligomers play an important role in triggering the apoptosis of neurons in AD in a similar way to what occurs in RGC death in animal models of glaucoma [16]. Although it is unclear whether soluble Aβ oligomers also contribute to the atrophy in age-related macular degeneration (ARMD), they have certainly been identified in the drusen, extracellular deposits considered hallmarks for ARMD [17]. In addition, hyperphosphorylated tau has been shown to accumulate in the RNFL of a transgenic mouse model bearing the P301 S tau mutation, which is associated with disruption of axonal transport and ganglion cell degeneration [7,18]. Thus, these findings suggest that abnormally processed and aggregated proteins such as tau or APP may be key players in causing the pathology seen within the eye of the AD patient. Although examination of the eye may become an important part of a diagnosis of AD, separating AD-related pathology from other ocular diseases, particularly glaucoma, will be a continuing challenge.

2.2. Neurochemistry deficiency in the AD retina

Acetylcholine deficiency is part of the pathology in AD patients [19]. There is presynaptic deterioration of cholinergic pyramidal neurons. Although several excitatory neurotransmitters have been associated with AD pathology (e.g., glutamate, noradrenaline, dopamine, and serotonin), cholinergic transmission seems to be the most affected. Cholinergic signaling in the retina is mediated by acetylcholine activating muscarinic and nicotinic receptors on ganglion cells [20,21]. The activity of acetylcholine in the retina is through the interaction of amacrine cells in neuronal feedback mechanisms [22], although there is no clear suggestion of altered cholinergic transmission in the retina of AD patients or its deficit in the visual pathway [23]. In fact, more direct tests of visual function conducted by Strenn et al [24] on AD patients tested for pattern, scotopic, and photopic luminance electroretinograms did not show any differences compared with age-matched normal people as to suggest neurochemical retinal deficit in AD.

3. Structural changes of the retina, optic nerve, and lens in AD and their potential as biomarkers for diagnosis of AD

3.1. Retina and optic nerve

There has been great interest in the eye as a source of potential biomarkers for the diagnosis of AD patients. Abnormalities in the ONH and retina in AD were first reported by Hinton [10]. In a postmortem histological examination of the retina and optic nerve of four patients with AD, they showed thinning of the ONH and ganglion cell loss. More recently, several studies have identified thinning of the peripapillary RNFL in AD patients using in vivo optical imaging techniques such as optical coherence tomography (OCT) scanning laser ophthalmoscopy and scanning laser polarimetry. This measurement of the RNFL in vivo is a potential biomarker for AD. The OCT quickly acquires cross-sectional images of the retina with little cooperation required from the patient. Therefore, because of its ease of administration, the OCT is likely to play an important role in diagnosing and managing AD. Paquet et al [11] used OCT to examine RNFL thickness in patients with amnestic mild cognitive impairment (MCI; recognized as an early form of AD), mild AD, moderate to severe AD, and healthy age-matched controls. RNFL thickness was reduced in all three AD groups compared with controls. Among the increasing number of papers evaluating retinal thickness with OCT, Iseri et al [25] measured RNFL thickness, macular volume, and macular thickness in 14 patients with AD and 15 age-matched control subjects. They found that the RNFL average thickness was significantly lower in AD patients. Confirmed in many recent studies, the retinal thickness of the macula was reduced in the AD group and this thinning was most