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The Retina: A Different Perspective into Alzheimer's Disease Screening

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ABSTRACT

The field of identifying retinal biomarkers of Alzheimer's Disease has seen tremendous growth in recent years. The retina has great potential for being used in screening for Alzheimer's disease (AD); it is the only part of the CNS not shielded by bone, and AD patients have several visual complaints. A number of major biomarkers in the retina have been found, including retinal nerve fiber layer (RNFL) thinning, retinovascular changes, pericyte loss and blood-retinal barrier (BRB) weakening, β-Amyloid (Aβ) deposits, Hyperphosphorylated tau and neurofibrillary tangles (NFTs), and gliosis/inflammation. All of these parallel brain biomarkers. Furthermore, new ocular biomarkers have been found (the efficacy of which is not yet fully proven) - Aβ in the lens, choroid thinning, and visual symptoms. Amyloid biomarkers probably have the most potential among these for screening; however, a multivariable model will be more effective. In the future, the Atlas of Retinal Imaging in Alzheimer's Study (ARIAS) study, which has already commenced, will search for a wide range of retinal biomarkers in many patients in varying stages of AD and risk levels of AD; it will also explore the interrelationships between those biomarkers to find a potential multivariate screening test for AD. Also, tear fluid could be a potential future biomarker that will be relatively easy to screen. Overall, this field has made great strides in recent years, and has great potential for groundbreaking advances in the near future. The promise of course is to enable simple, inexpensive, widespread and regular screening for AD using retinal biomarkers.

Introduction

Alzheimer's Disease is a neurodegenerative disease that leads to dementia and eventual death. Typically, the patient experiences memory loss and reduced cognitive ability, followed by reduced ability to perform day-to-day tasks. The biggest differences between the brains of people with Alzheimer's and healthy patients' brains are β-amyloid (a protein) plaques, neurofibrillary tangles (formed by proteins), and structural degeneration, all three of which are present in Alzheimer's patients, but none of which are present in normal brains. Current clinical diagnosis involves methods that are either too risky or impractical to be done often. However, the retina, as the only portion of the CNS not shielded by bone, could offer a window into Alzheimer's Disease. Pathologies similar to those in the brain have already been identified there; hence, examining the retina would offer more practical screening possibilities. While this paper focuses primarily on retinal markers, there are some promising non-retinal ocular markers and those are briefly covered.

Alzheimer's Disease

Alzheimer's Disease (AD) is the most common neurodegenerative disorder in the world, with 50 million [2] patients worldwide. It causes memory loss and then reduced cognitive abilities, though some individuals in their 40s and 50s

develop a variant of Alzheimer's that starts with visual symptoms [3]. The damage caused by Alzheimer's is typically irreversible, and it is often a terminal disease. The risk of developing Alzheimer's doubles every 5.9 years, with about 1 in 5 individuals over 85 years old [3] suffering from AD. Alzheimer's progresses in three stages; the preclinical stage, which is an insidious process that takes decades, the mild cognitive impairment (MCI) stage, and dementia. In the first stage, no symptoms show; in the second stage, memory begins to deteriorate, and cognition starts to decline, while in the last stage, ability to perform day-to-day tasks is impaired. Currently, Alzheimer's can only be diagnosed as post-mortem; this is why trackable biomarkers are needed to identify and measure the progression of Alzheimer's. In the brain, it is known that β-amyloid plaques (Aβ) form due to abnormal processing of amyloid precursor protein (APP), a membrane protein found in neurons. Furthermore, tau proteins, which are cytoskeletal proteins in neurons, form neurofibrillary tangles (NFT); this tangling up of tau in turn causes neuronal death. Furthermore, it is known that amyloid plaques clog up cerebral blood vessels, and so do collagen tangles [4], hence obstructing cerebral blood flow. The most common theory of Alzheimer's progression begins with mass amyloid deposition during the preclinical stage along with the formation of NFTs, driving neuronal loss [1]. Structural degeneration and memory symptoms start to show as MCI begins; clinical function gets impaired as MCI progresses into dementia, while structural degeneration increases [1]**.** It is worth noting that most of the Aβ plaques form during the preclinical stage, as do a sizable portion of NFTs (see **Figure 1**) [1]. Soluble Aβ also exists in the CSF [2]; other theories implicate this rather than Aβ plaques as the main indicator of AD. However, the first theory is the most widely accepted, and we shall adopt that here.

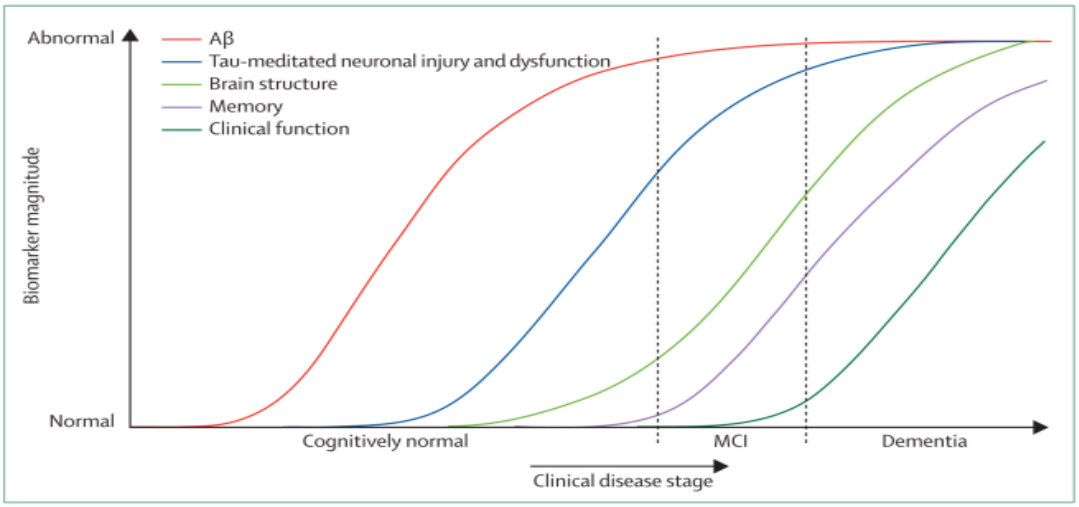

Figure 1. Biomarker magnitudes through AD progression (Jack et al., 2010)[1]

Alzheimer's disease is typically diagnosed when memory and cognitive symptoms begin to appear during the MCI stage. However, as illustrated in the past discussion and in **Figure 1**, most of the harmful processes are already set in motion by then. As a result, screening for, and possibly diagnosis of, Alzheimer's during the preclinical stage is very important, as current treatments can slow down the progression of Alzheimer's, and work best in early stages. Also, possible future treatments that can halt the progression of Alzheimer's will be most effective then. The current diagnosis methods primarily involve cerebrospinal fluid (CSF) extraction, an amyloid-detecting positron emission tomography (PET) scan, or an magnetic resonance imaging (MRI) scan. The first method finds biomarkers (CSF biomarkers include abnormal amyloid and tau levels) quite reliably [2], including biomarkers of preclinical AD, but uses highly invasive and risky lumbar punctures that cannot be performed that often. Amyloid-detecting PET involves exposure to large amounts of radiation [3], and hence also cannot be performed regularly. Also, it tends to miss smaller plaques and soluble amyloids [2]. MRI can detect only structural degeneration, and by the time that happens, the neuro-degeneration has already progressed enough to cause major clinical symptoms. As a result, a method of screening that is non-invasive, low-cost, and low-risk that can be performed regularly (about once a year) is needed.

The Case for Considering Retinal AD

Why should the retina be considered for AD screening? Visual deficits in Alzheimer's patients have been measured, such as visual field loss [6], visual acuity reduction [6], impairments with fixation on a target [6], and impaired ability to perform complex visual tasks [6] (such as reading). As the only part of the CNS that is not shielded by bone, and as part of the eye, which is relatively easy to image and look at, the retina has great potential for being a site of visualization and possible screening of Alzheimer's should biomarkers manifest there[7,14]. Having said that, this paper also lists some promising non-retinal markers (for example, micro-RNA and proteins in tears [3,12,13]).

State of the Art in Retinal and other Ocular Biomarkers

Retinal Biomarkers

Retinal nerve fiber layer (RNFL) and retinovascular biomarkers

A key study of retinas of early Alzheimer's patients revealed significant RNFL thinning in the superior quadrant, as compared to healthy control patients [4]. Thinning was also observed in the inferior region, but it was not statistically significant [4]. Furthermore, retinal blood vessels were observed to have narrowed in Alzheimer's disease [4], and blood flow significantly decreased [4]. Optical coherence tomography (OCT) (A noninvasive imaging technique using near-infrared light to obtain high-resolution cross-sectional images) was used to image the retinas of these patients in order to determine thickness of the RNFL, while bidirectional laser doppler velocimetry was used to determine blood flow and vessel diameter. Unfortunately, that study was limited by the fact that it only had 9 participants in the experimental group [4]. Nevertheless, these findings are revolutionary, and several other studies corroborated this [2]. Vessel tortuosity (how twisted they are) was also found to have increased in AD patients [3], and ganglion cell degeneration has also been reported by several studies [2, 3]. OCT has been demonstrated to be of great utility for visualizing the retina, and it is fairly low cost. Hence, this is certainly a viable method for inclusion in a possible ocular screening test for AD. Furthermore, using optical coherence tomography angiography (OCTA), retinal blood vessel imaging has become easier and more accurate since the first study. See **Figure 2** to see some retinovascular differences between healthy patients and patients with AD [9,12]. However, RNFL thinning is also observed in common eye disorders such as glaucoma, and differentiation of AD-induced retinovascular complications from the more likely culprits, vascular diseases, is difficult [3]; these are the limitations of biomarkers of this nature.

However, despite these limitations in differentiating AD from vascular conditions, a recent ML study was able to classify Alzheimer's patients' retinas from non-AD retinas with an 82.44% accuracy rate [5]. It used retinal images from a large-scale clinical database, the UK biobank, and classified them based on retinovascular characteristics [5]. The algorithm also generated a saliency map, which determined that effects in smaller blood vessels are more significant than changes in larger blood vessels in checking for Alzheimer's [5]. There is potential for these biomarkers to be used in AD screening, despite their limitations.

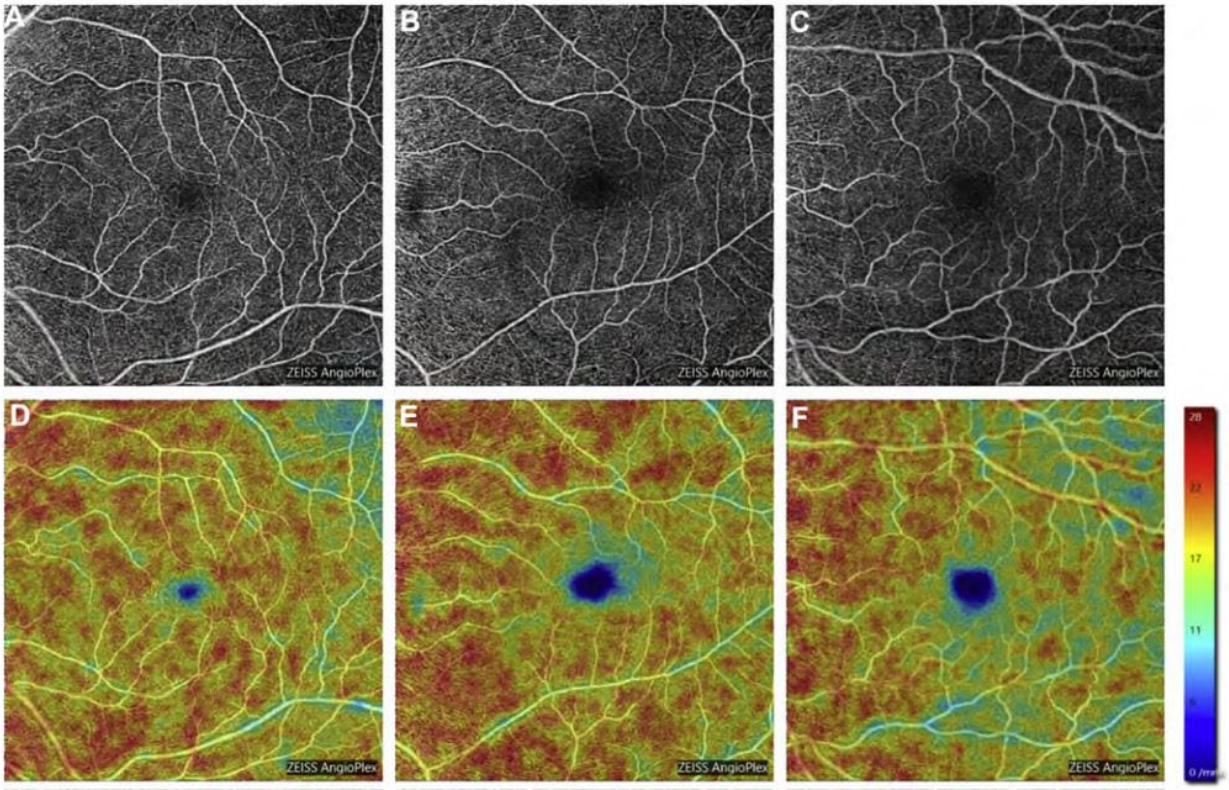

Figure 2. Retinovascular changes in AD patients. This image shows the differences between the retinas of a cognitively healthy adult (column1), a mildly impaired adult (column 2) and an AD patient (column 3) in terms of blood vessel density. Blue represents fewer blood vessels and red more. (Yoon et. al)[12]

Pericyte Loss

Pericyte loss has also been found in retinas of patients with AD [2], along with weakening of the BRB [2]. Pericytes are cells found just outside blood vessels which regulate blood flow and also are part of the BBB and BRB. Their degeneration has actually also been correlated with MMSE scores [2] (state mental health exams). Their degeneration can also in part explain the retinovascular anomalies that have been discovered to accompany AD. In addition, their degeneration results in the weakening of the BRB.

Aβ presence in the retina

Even more significantly, Aβ plaques have actually been found inside the retinas of AD patients [2,3]. Several studies have found plenty of extracellular deposits of Aβ in the retinas of AD patients [3]. Aβ plaques in the retina are typically smaller than the ones in the brain (see **Figure 3** for comparison of the plaques), but the burden on the retina is similar to that on the brain [2] . Furthermore, Aβ amount in the retina is associated with the amount of Aβ in the brain, especially with the visual cortex [2]. One method researchers used to find Aβ deposits in the brain was using curcumin [3], which is a natural chemical that binds to Aβ and fluoresces (see **Figure 4** for how this would look) [3,9] making it easier to find Aβ using a microscope. Researchers also use hyperspectral imaging to see amyloid plaques [3]. This technique measures tissue reflectance to a wide range of incident wavelengths; [3] amyloid has been determined to have a unique hyperspectral signature ex vivo, and further in vivo studies have confirmed that [3]. Aβ deposits have been found in both the ganglion cell layer and the RNFL. Furthermore, Aβ primarily concentrates in the superior and inferior quadrants of the retina [2]. This in fact correlates with the earlier findings that the RNFL thins the most in the superior and inferior quadrants in AD patients [4] . A few studies have also found small amounts of Aβ in their control groups [3], but this is

hypothesized to be attributed to the presence of very early-stage Alzheimer's patients, who are undiagnosed, in the control group. In fact, this error is quite important, as it could potentially show the fact that Aβ plaques begin to deposit in the retina early on, implying that early screening and potential diagnosis is possible with these methods. This is an exciting possibility that warrants future investigation [9,12,13]. See **Figure 5** for the relative locations and concentrations of Amyloids over time.

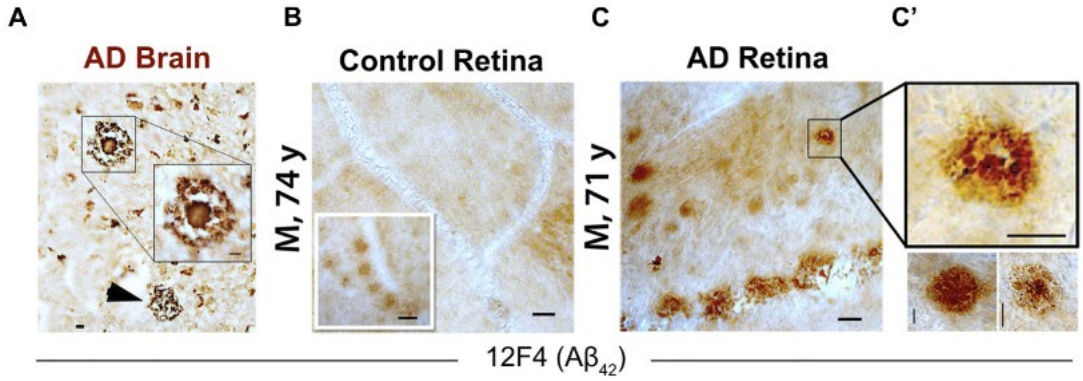

Figure 3. Amyloids in the brain and the retina. This picture shows Aβ plaques in the brain and in the retina. This also shows a healthy person's retina for comparison. (Mirzaei et al., 2020) [2]

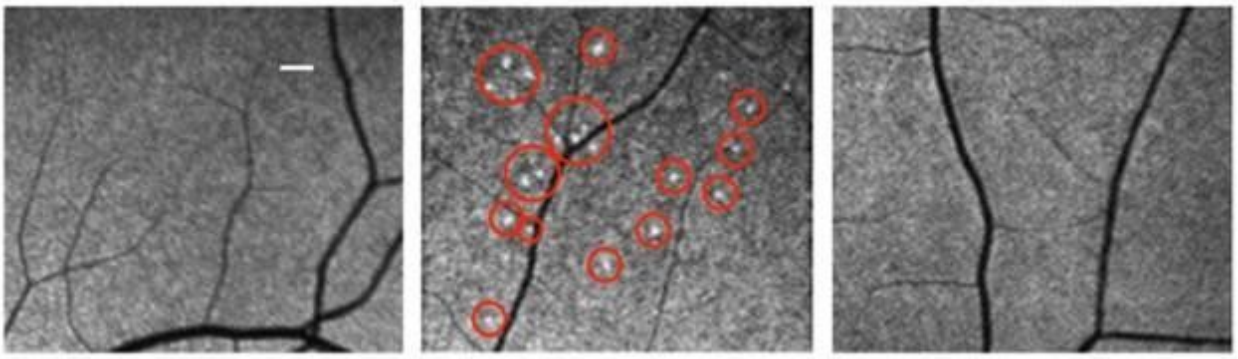

Figure 4. Curcumin-based imaging. The middle image is of an AD patient, while the left image is of a healthy control, while the right image is of a patient with vascular image. This shows that Aβ detection is both sensitive and specific. (Koronyo et al. 2017)[9]

Tau and NFTs in the retina

Hyperphosphorylated tau proteins and NFTs have also been found in the retinas of patients with AD [2]. In fact, Hyperphosphorylated tau has been found the most in exactly the areas with most nerve degeneration in the retina [2]. However, unfortunately, due to lack of method standardization, many studies conflict with each other about tauopathy in the retina[2]. **Figure 5** shows where and when tau proteins and NFTs may form.

Gliosis and retinal inflammation

Retinal inflammation and gliosis have also been observed in AD patients[2]. In the brain, it is known that astrocytes and microglia, two types of glial cells, activate and cause the inflammatory response. Astrocytes and microglia can function as immune cells. They have high neurotoxicity (ability to kill neurons that they deem as "infected") and facilitate synaptic pruning, and this potentially causes some neuronal death and cognitive function loss [2]. Retinal inflammation and glial cell activation has been seen in postmortem studies of AD patients and animal studies [2]. In fact, this could

potentially relate to pericyte loss, as pericyte loss causes blood-retinal barrier weakening, which could lead to immune glial activation. **Figure 5** shows where and when gliosis may occur.

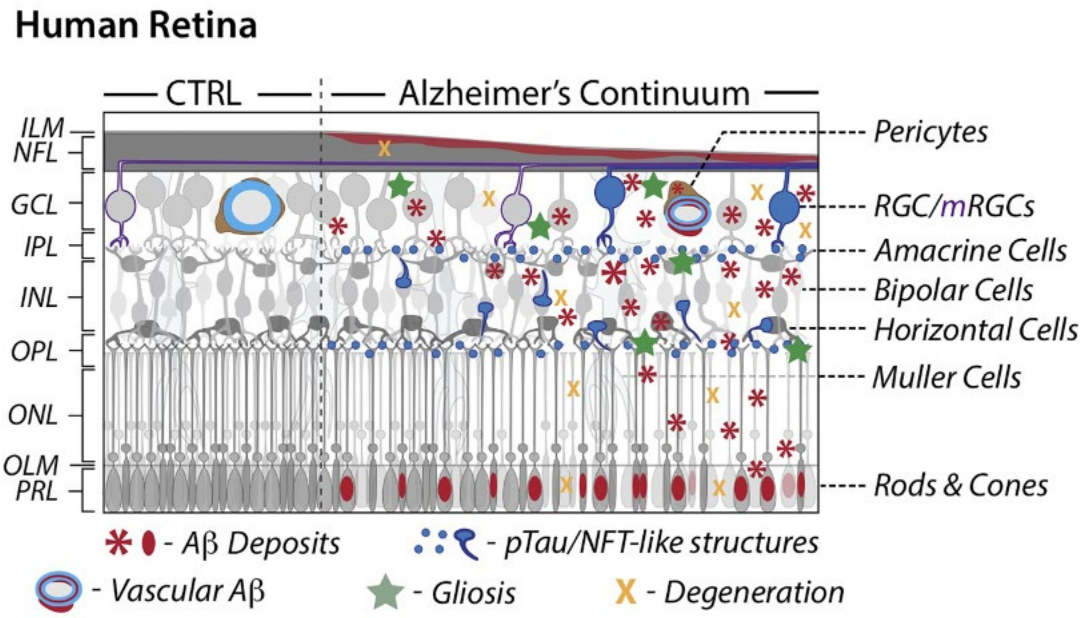

Figure 5. AD biomarkers in retina. This is a schematic of the progression of AD and the relative time of appearance and amounts of individual AD biomarkers in the retina. This sums up much of the earlier discussions about retinal biomarkers. CTRL stands for control (when the patient is healthy), and the acronyms on the left represent the 9 retinal layers. The retina has 9 layers; from inside to outside, they are; ILM (inner limiting membrane), NFL (nerve fiber layer), GCL (ganglion cell layer), IPL (inner plexiform layer), INL (inner nuclear layer), OPL (outer plexiform layer), ONL (outer nuclear layer), OLM (outer limiting membrane), PRL(photoreceptor layer). (Mirzaei et al., 2020)[2]

Retinal biomarkers and screening for AD

Not much work has been done on finding a screening test for Alzheimer's based on these retinal biomarkers, but we can develop some basic criteria. The biomarkers that are screened need to be fairly specific to Alzheimer's, and relatively easy to measure using cost-effective methods that are widely available. Direct visual tests (where a patient is supposed to perform a given visual task) will not be that effective, as they are highly nonspecific, and by the time AD causes visual abnormalities, it is too late. Techniques such as OCT and its close relatives (OCT angiography, etc.) are all fairly common, but these techniques only pick up changes in RNFL thickness and retinovascular parameters. These are both not specific for AD; glaucoma, for instance, can also cause RNFL thinning and abnormalities in retinal blood vessels. Aβ is a specific biomarker for Alzheimer's Disease; however, hyperspectral imaging is not widely used in eye clinics yet. Fortunately, hyperspectral imaging is gaining traction in eye clinics, so it is a distinct possibility that in the relatively near future, this will be fairly common. Then, Aβ imaging with hyperspectral techniques, possibly in conjunction with OCT, would provide a good screening test. This is certainly a practical possibility worth exploring. Another possibility could involve imaging retinal blood vessels; despite the non-specificity, the ML study has shown with its high accuracy that this has potential. However, a lot more correlated data is needed for any biomarker before it becomes a viable screening option.

Non-Retinal Ocular Biomarkers

Beyond the retina, there are other ocular biomarkers for AD that hold promise for disease screening and progression. Some of the most promising are described below.

Choroidal thinning

The choroid, which lies between the sclera and the retina, contains blood vessels which nourish the outer layers of the retina. Choroid thinning has been found by a factor of 20-30% in AD patients compared to healthy controls according to a few studies[3]. However, choroid thickness fluctuates with time of the day, and it also reduces due to aging and some vascular conditions; hence, it is not a specific biomarker, and is highly volatile.

Lens clouding

The lens has actually been found to contain Aβ plaques in 85% of AD patients, according to one study [3]. These so-called "AD cataracts" have also been found in transgenic AD mice [3]. However, they cause no visual symptoms for patients; a full dilation is needed to see them[3] , so detecting them in patients is a matter of chance. Studies also conflict about the existence of these plaques [3], and it is unknown whether one can identify the stage of AD in a patient by looking at this. Recently, Lanosterol, which is present in over-the-counter medicines for cataracts, has shown a reduction of Aβ plaque aggregation [10]. Given this, a biomarker that can quantify lens clouding certainly needs more exploring.

Abnormal pupillary response

The pupillary response is also impaired in AD patients [3, 6]. When more light enters the eye, the pupil contracts, while the pupil dilates when the surroundings are dark. However, researchers have found a reduction in the pupillary response when room illumination is changed abruptly or the eye is flashed [3]. However, the changes are quite subtle, and hard to measure [3]. As a result, this may be impractical in a clinical setting. However, ways to amplify the difference are being explored, and this has potential in being a biomarker.

Visual abnormalities in AD

There are several direct visual manifestations of AD in patients. Typically, AD patients experience reduced contrast sensitivity[6] and an impaired ability to focus on track objects[6], especially moving ones. AD patients also have visual field deficits [6], and are unable to perform complex visual tasks, such as reading [3, 6]. Also, about 50% of patients have color vision loss, and about 20% of patients experience visual hallucinations [6]. These can be considered as biomarkers, even though they are nonspecific for AD.

Tear fluid-based markers

There is one other potential biomarker that could have significant implications if it is proven to identify AD onset. There is reason to believe that tear fluid can actually be different in AD patients [3]. Proteomic studies of the aqueous humor have revealed some AD-specific proteins in patients with AD [3]. While aqueous humor extraction itself is very invasive (and hence, not a viable primary screening option), that gives reason to believe that tear fluid can contain AD-specific molecules in AD patients. Tear fluid has also shown promise in detecting other neurodegenerative conditions such as glaucoma [3]. Micro-RNA would be the defining molecule in tear fluid that can serve as a potential AD biomarker [3]. Micro-RNA is a noncoding type of RNA that modifies gene expression at the post-transcriptional level and has been isolated in tears [3]. Certain types of micro-RNA have been determined to take part in amyloid processing [3]. Hence, micro-RNA samples from tears certainly warrant further analysis; future studies should analyze these samples in AD patients and healthy controls to determine if this is a viable biomarker. If proven to be a valid biomarker, the implications of tear fluid testing in screening for Alzheimer's will be very significant, as it will be much easier to extract and analyze tear samples than performing the other methods outlined above. This is further supported by another study, where significant changes in flow rate and protein content were observed in tear samples from AD patients[11]. This is due to alterations in the chemical barrier in AD patients' tears[11]. In particular, a combination of four proteins (lipocalin-1, dermcidin, lysozyme-C and glycoprotein lacritin) were shown to be highly effective as a potential biomarker [11].

Discussion

Currently, the single biggest issue impairing the use of retinal and ocular biomarkers in screening is the lack of data for many of them, including tau proteins, gliosis, pericyte loss, choroidal thinning, lens clouding, and the pupillary response. There is conflict as to whether many of the biomarkers discussed here are present in the retina or not, due to lack of standardization of methods [3], even the ones with a lot of promise, such as amyloid detection, need more supporting data. Furthermore, past studies have only studied a single retinal biomarker at a time; a multivariate screening model is more likely to be specific and sensitive for AD than a single biomarker method. As a result, a study that finds the interactions between various retinal (and other ocular) biomarkers of AD is needed. A new study, Atlas of Retinal Imaging in Alzheimer's Study (ARIAS) [8], currently in its infancy, is underway. It aims to create a large database consisting of imaging of various types to find various retinal AD biomarkers in patients' retinas [8]. The study will include patients who are at low risk for AD, high risk for AD, with MCI, and in the earlier dementia stages. The patients will be checked over the course of several years, and the progression of retinal biomarkers (and cognitive symptoms) will be monitored. The final goal would be to potentially find a multivariate screening test based on these results [8]. This study could potentially revolutionize the screening of Alzheimer's.

In the meanwhile, techniques that have potential for screening Alzheimer's, such as hyperspectral imaging, should be made widely available. This is because accessibility is a major factor in a good screening test. Also, the ML study should be replicated, and the same model should also be tested on other databases (ARIAS would make a good testing database after its completion); as this method warrants more investigation due to its high potential. In the meantime, newer biomarkers should be explored, and the data generated from ARIAS will help researchers find more biomarkers[8].

Conclusion

In this paper, we have reviewed various ocular/retinal markers which show potential for identifying Alzheimer's disease progression. Several of these have potential for being used as a screening mechanism in an eye exam. While there is great promise in this field, further work is needed in establishing the efficacy (sensitivity and specificity) of these markers.

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