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Retinal Examination with Curcumin in Alzheimer's Disease

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Abstract

Background: Currently there is no definite cure for Alzheimer's therefore early detection is critical. Undetected Alzheimer's disease (AD) can lead to severe accidents, neglecting to take essential medications, injury to oneself or others, and/or financial problems. Currently, biomarkers are the most promising way to detect Alzheimer's early on.

Biomarkers such as beta-Amyloid and tau levels taken through invasive methods or brain scans that involve radiation are among them.

Objectives: Alzheimer's disease (AD) presents itself in the body with an increase in β-Amyloid (Aβ) plaque deposition, Neurofibrillary Tangle formation (NFT), and inflammation. As the retina is an extension of the brain and the brain structure it is possible to detect misfolded proteins *via* retinal examination non-invasively. One of the main objectives of this study is to determine the effectiveness of curcumin which is a phytochemical which can bind to Amyloid-beta and Tau and can be used both for the diagnosis and early treatment of AD. The aim of this study was to discover the binding property of curcumin to both Tau and AB in the retina as a potential biomarker for AD.

Methods: In this study, 20 patients were invited with mild AD who had undergone retinal examination within the past 2 years. All the patients had retinal imaging with curcumin which revealed misfolded proteins during the examination and then they were advised to take daily curcumin. The mean age of the patients was 71, and the patients were instructed to take Curcumin Meriva in 500 mg supplements once daily after their prior examinations. All patients had tests repeated with FAF and Heidelberg Spectral is OCT device. The regions with abnormal lesions on FAF were detected and the layer of the defect was scanned by OCT plus compared with the previous imaging of the patients. The images were examined in a masked fashion by 2 specialists.

Results: The images disclosed hyperfluorescent lesions on FAF and OCT revealed accumulations in the inner layers of the retina. Some accumulations had dot shapes and others had fibril-tangle shapes. Some lesions were present in prior exams, but they were more pronounced and shinier after curcumin use. Their size and shape were in concordance with misfolded proteins in the brain.

Conclusion: Retinal examination with curcumin revealed AB plaques in the retina in prior studies. Our study is the first that may demonstrate an easy way to detect the culprit plaque Tau inside the retina of live patients.

Keywords: Alzheimer's disease; Curcumin; Neurofibrillary tangle formation; Inflammation; Retina; β-Amyloid (Aβ); Misfolded proteins; Tau

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Abbreviations

FAF: Fundus Autofluorescence; OCT: Optical Coherence Tomography; APP; NFT: Neurofibrillary Tangle Formation; RPE; CAA: Cerebral Amyloid Angiopathy

Introduction

Currently Alzheimer's disease (AD) has no definite cure and early detection is the most proactive step regarding this disease. One-third of all Alzheimer's diagnoses occur nearly three years after the first symptoms appear.

Early diagnosis and early treatment can be achieved *via* the retina which is an extension of the brain, and it is able to show changes in the brain's structure. Studies show that biomarkers found in blood and cerebrospinal fluid are also coming to light for early detection of AD. Recent studies have demonstrated that the accumulation of the smaller, soluble and dynamic tau oligomers, Amyloid beta as well as neuronal loss and inflammation occur in AD In this study curcumin is used as a

potential biomarker for AD. Curcumin is a substance that is found in turmeric and makes up about 2% to 5% of the turmeric plant f Bioavailability [1].

Researchers have found that curcumin is a potential neuroprotective substance *in vitro* and i*n vivo* trial. Other studies suggest that it may have preventive effects of AD development due to its being anti-inflammatory. This study aims to discover early detection strategies of AD with curcumin [2].

Fundus autofluorescence can detect lipofuscin in the retina, and this signal from the retinal pigment epithelial cell is correlated with lipofuscin content. The autofluorescence is increased with RPE dysfunction due to the accumulation of lipofuscin. On the contrary, the FAF signal is decreased in the setting of RPE or photoreceptor loss [3]. With the emergence of the confocal scanning laser technology OCT has made approaches clinically relevant. *Via* confocal SLO a fast-moving, focused, low powered laser is swept across the fundus in a pattern. The confocal nature ensures that reflectance is from the same optical plane [3].

In patients' evaluations with AD, FAF examination detects hyperfluorescent (regions with excessive lipofuscin) or hypo fluorescent (atrophic retina) areas. This being said, neurodegeneration may cause lipofuscin deposition in different layers of the retina. To identify the layer of defect, OCT is performed taking the abnormal areas on FAF into consideration. To better understand the nature of the lesion, curcumin may be orally or intravenously administered. Curcumin has various biological effects and is a yellow phytochemical in the rhizome of *Curcuma longa* which is used as an Indian spice. Epidemiological studies suggest that a curcumin-rich diet might decrease the risk of developing AD [4].

The binding of curcumin to Senile Plaques (SPs) in Cerebral Amyloid Angiopathy (CAA) was examined. The aged brain of various animal species and a human patient with AD were studied. Together with its binding Neurofibrillary Tangles (NFTs), brain sections were immune stained with anti-Amyloid β protein 1-42 (Aβ42) and anti-Amyloid β protein 1-40 (Aβ40) antibodies. Curcumin specifically binded to the aggregated Aβ molecules in various animals, and further to phosphorylated tau protein (Figure 1), probably most likely due to its conformational nature.

A study aimed to characterize curcumin-fluorescent yellow curry pigment-labeling of neuronal Fibrillar Tau Inclusions (FTIs) in representative cases of tauopathies. After the identification of FTIs in hematoxylin and eosin-stained brain sections, sequential labeling and signal colocalization image analysis was used to compare curcumin with monoclonal antibody AT8 immunofluorescence. As well as Gallyas silver staining by visualizing the same FTIs. Curcumin proved highly comparable to ThS and Gallyas staining in the detection of FTIs in AD. The results provided evidence that it's binding to tau aggregates in diagnostic pathology and *in vivo* [5]. Curcumin's bioavailability is poor in humans and with the addition of black pepper; it is able to increase its absorption [6].

Curcumin with Meriva is the lecithinated form and has 29 times more absorption capacity and is used for oral delivery in many supplements [7].

Materials and Methods

In this study, 20 patients were invited with mild AD who had undergone retinal examination within the past 2 years. All the patients had retinal imaging with curcumin which revealed misfolded proteins during the examination and then they were advised to take daily curcumin [8,9]. The mean age of the patients was 71, and the patients were instructed to take Curcumin Meriva in 500 mg supplements once daily after their prior examinations. All patients had tests repeated with FAF and Heidelberg Spectral is OCT device. The regions with abnormal lesions on FAF were detected and the layer of the accumulation was picked up by OCT plus compared with the previous imaging of the patients. The images were examined in a masked fashion by 2 specialists.

Results and Discussion

Some lesions were present in prior exams, but they were more pronounced and shinier after curcumin use. Their size and shape were in concordance with misfolded proteins in the brain (Figure 2).

The images disclosed hyperfluorescent lesions on FAF, and OCT revealed accumulations in the inner layers of the retina. Some consisted of accumulations of dot shapes while others had fibril-tangle shapes. Studies suggest that retinal Amyloid burden is correlated with brain Amyloid burden in AD. Moreover, it has been proven that retinal accumulations appear before they start to invade the hippocampus (Figures 3-6) [10].

Hyperfluorescent lesions were highlighted on FAF, and OCT revealed accumulations in the inner layers of the retina. Curcumin revealed lesions which had similar shape and size with Tau tangles. Screening Amyloid beta in the retina is certainly a breakthrough in AD [11]. Imaging the retina is easy, non-invasive, cheap, and does not involve radiation. In prior studies retinal examination with curcumin revealed AB plaques in the retina [11].

There are two questions that come to mind when considering the recent developments in AD studies:

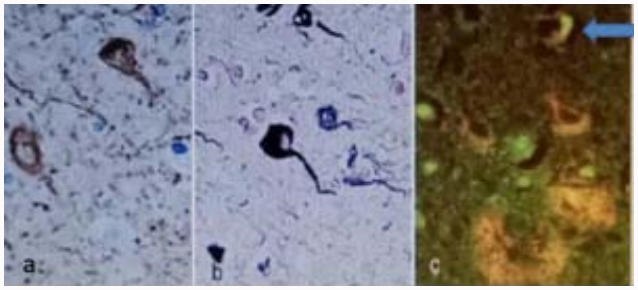

Figure 1: Curcumin binding to Tau in mouse brain (black tangles show Tau accumulation, the arrow in the colored image points out yellow curcumin binding to Tau).

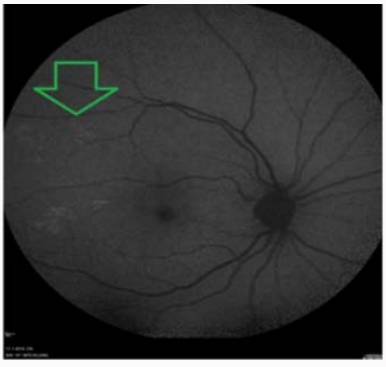

Figure 2: Hyperfluorescent lesions on FAF.

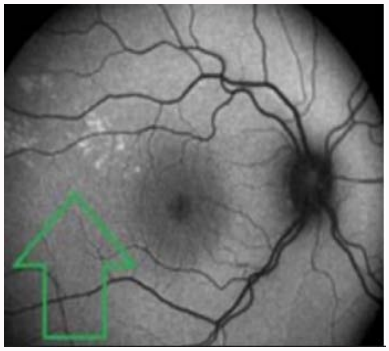

Figure 3: Hyperfluorescent lesions on FAF.

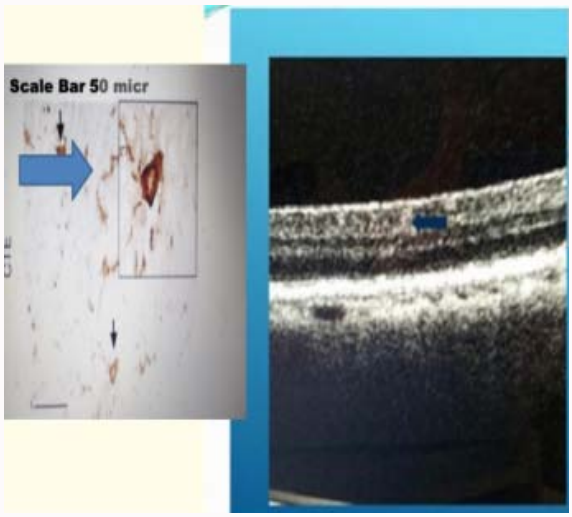

Figure 4: Accumulations suggestive of Tau on OCT.

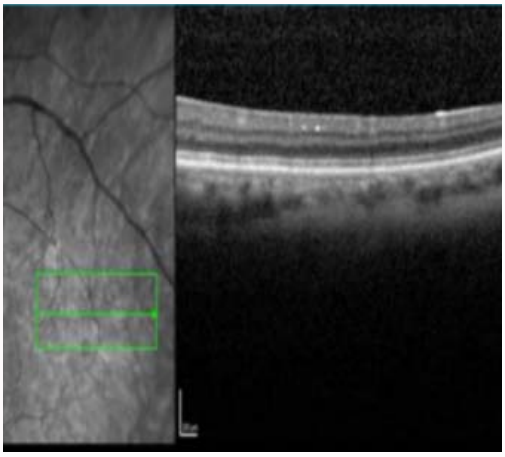

Figure 5: Accumulations suggestive of A. Beta on OCT.

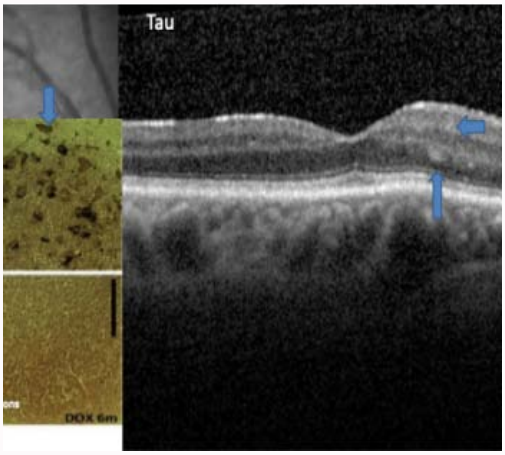

Figure 6: Accumulations suggestive of Tau on OCT.

1. A Mayo Clinic study of thousands of brains revealed Tau as a driver of AD. Therefore, is there a need to show Tau protein along with AB in the retina in order to make correct assumptions about the disease process [12]?

2. Approximately 30% of people who do not have any signs of dementia have brains "chock-full" of AB at autopsy [13].

The presence of AB may not be enough to prove that every patient will develop the disease in the future. The increased deposition of AB isoforms has been described on photoreceptor outer segments, and alongside the RPE–Bruch's membrane interface in the aging human and mouse retina. Another study using immunostaining revealed AB on the outer segments of photoreceptors all throughout the retina in humans as an aging process [14]. This deposition process may very well only be a sign of aging and not related to AD. Analyses of drusen components have shown the deposition of AB within vesicles in the eyes of age-related maculopathy patients [15].

Another approach may be demonstrating and quantifying both proteins in the retina. In the brain, tau deposits have been found in the temporal lobe early in the disease. Tau PET can be used to detect early AD, but it involves radiation. Neuroinflammation is another factor in the etiopathogenesis of neuroinflammatory diseases [16].

In a detailed retinal examination, hypo fluorescent areas on FAF show atrophic retinal changes which may indicate an advanced stage of the disease. Hyperfluorescent lesions contain more lipofuscin, but the retina may be less compromised and not atrophic. Hyperfluorescent dots on FAF become more noticeable after curcumin use, proving that it has an affinity for β-Amyloid and Tau. An examination of the retina with FAF and OCT provides valuable results about neurodegeneration which may make these tests trustable biomarkers for AD. It may be possible to detect the disease while also examining the progression of the lesions [17,18].

It is also worth stating that plaques giving the impression of Amyloid beta are more prominent in the retinal periphery while Tau like tangles are more pronounced at the posterior pole.

Conclusion

Retinal examination with curcumin revealed AB plaques in the retina in prior studies. Our study is the first in which to also demonstrate that by using FAF and OCT in patients who take daily curcumin, culprit plaque tau may be shown along with AB in the retina of live patients.

With the consideration of no proven treatment of AD, curcumin may be considered for prevention as well as diagnosis and monitoring being a functional food [19,20]. In our study, Curcumin Meriva was taken in 500 mg supplements once daily for a prolonged time up to 2 years without important side effects [21].

The main contribution of our study to the existing ones may be the

detection of curcumin-stained lesions similar to Tau accumulations in the retina and monitorization of them for 2 years.

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