Original Research Paper

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MISFOLDED TAU IN THE RETINA

Umur A. Kayabasi Department of Neuro-ophthalmology, Bahcesehir University Istanbul / Turkey

ABSTRACT **INTRODUCTION:** Tau protein plays a crucial role in many neurodegenerative diseases including Alzheimer's disease (AD). Tau inclusions and amyloid beta (AB) depositions have been described in the post-mortem retina exams of AD patients. Cryo-electron microscopy (Cryo EM) was recently used to detect the detailed structure of Tau filaments.
METHODS AND RESULT: We examined the retinas of PET-proven live AD patients by spectral domain optical scanning tomography (SD-OCT) and fundus autofluorescein (FAF). The hyper or hypofluorescent lesions in the retina were scanned by OCT and images that completely corresponded with the histopathological and Cryo- EM shapes of Tau filaments were observed.
CONCLUSION: Retinal Tau is a very promising target to detect early changes in AD and retinal imaging may be an exciting and trustable technique to predict and monitor the disease

KEYWORDS : Tau; OCT; Retina; Alzheimer's

INTRODUCTION

Tau protein plays a crucial role in many neurodegenerative diseases including Alzheimer's disease (AD). Tau dysfunction includes abnormal tau phosphorylation, protein aggregation, neurofibrillary tangle formation and neurotoxicity [1]. The retina is integrated with the central nervous system (CNS) and has been considered a window to the brain. Similar neurodegenerative processes affect the retina causing impaired contrast sensitivity, reduced visual acuity and abnormal motion perception. Approximately 50% of AD patients present with visual deficits that go along with RGC loss, thinning of the retinal nerve fiber layer, abnormal electroretinogram response and reduced blood flow [2]. Tau inclusions and amyloid beta (AB) deposition have been described in the post-mortem retina exams of AD patients. Phosphorylated and misfolded Tau accumulation has also been observed in RGC soma, dendrites and intraretinal axons in animal models. These pathological changes may cause retinal neuron dysfunction and subsequent death and suggest a prominent role for abnormal tau in visual deficits [2].

CRYO- ELECTRON MICROSCOPY

Cryo- electron microscopy (Cryo- EM) was recently used to detect the detailed structure of Tau filaments [3]. The researchers discovered C-shaped paired helical filaments (PHF) composed of Tau- subunits in the brains of live AD patients and they presented the C-shape in striking detail (Figure 1). Tau aggregation consisted of a mixture of PHFs and straight filaments (SF), the former making up about 90 percent of the total [3]. A C-shaped core defined the common proto filament of PHFs and SFs although the two Cs could have been arranged differently (Figure 2).

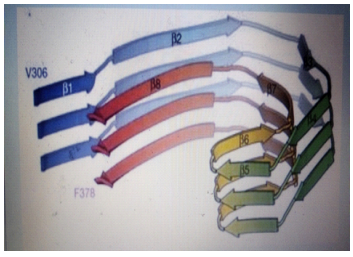

Fig 1 : C- Shaped Tau, Credit And Permission: Scheres Group Mrc-lmb.

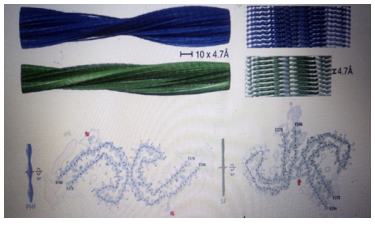

Fig 2 : - Phfs And Sfs, Credit And Permission: Scheres Group Mrc-lmb.

RETINAL IMAGING OF TAU

The retinas of PET-proven live AD patients were examined by spectral domain optical scanning tomography(SD- OCT) and fundus autofluorescein (FAF). The hyper or hypofluorescent lesions in the retina were scanned .by
OCT and images that completely.corresponded with the histopathological. and Cryo EM shapes of Tau filaments were observed.

Neurofibrillary tangles (NFTs) that were identical with the histopathological images in terms of shape and diameter were detected (Figures 3 &4 &5)

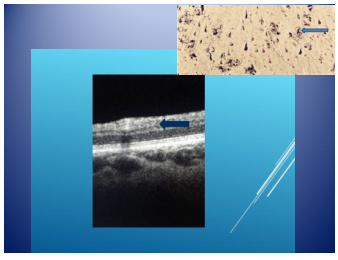

Figure 3: Sd- Oct Image And Histopathologic View Of A Nft.

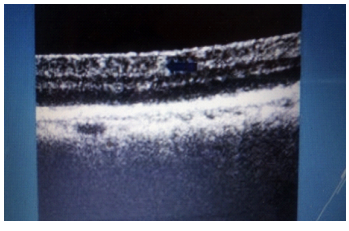

Figure 4: SD- OCT image of another NFT.

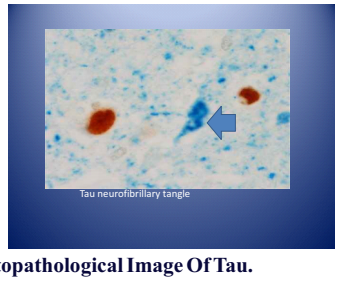

Figure 5 : Histopathological Image Of Tau.

DISCUSSION AND CONCLUSION

Some investigators found BA plaques in AD patients using different retinal examination techniques [4]. Others have shown retinal nerve fiber layer thinning by OCT due to AD . But, tau tangles were not shown in the retinas of live AD patients before, to the best of our knowledge. Our retinal tests easily disclosed accumulations which

seemed to be consistent with Tau tangle deposits. We also believe that exactly the same kind of toxic proteins aggregate both in the retina and brain. Since the retina is a direct extension of the brain, any lesion detected in the retina may be the reflection of a central nervous system disease. Maya Koronyo and her colleagues stated that retinal lesions started either earlier than or at the same time (but, not later) with the brain lesions and this would be many years before the clinical symptoms of AD arose [4]. Another unproven hypothesis was the migration of the toxic proteins from the retina to the brain via the optic nerve or vice versa [4]. Recent research revealed the importance of Tau aggregation in the disease process. The spread of tau protein aggregates in the brain correlated with clinically observed cognitive deficit and progression of functional brain scan deficit. The basis for this neuroanatomical spread was established in mouse models where abnormal tau could be exchanged between neurons. The early stage aggregates of tau (oligomers) acted as infectious particles, spreading the pathology from one region to the next [5].

Since the eye is the most easily access able part of CNS, retinal exam is quick, non-invasive and no radiation is involved. .The results of a very important study revealed that in a group of patients with mild cognitive. impairment and full-blown AD dementia, although all patients had extensive amyloid plaques, their brain amount of Tau was highly individual [6].

This finding could explain why the disease progressed at such a varying rate from one patient to the other stressing the importance of Tau in AD. Retinal Tau is a very promising target .to detect early changes in AD and retinal imaging may be an exciting and trustable technique to predict and monitor the disease.

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