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Fenestella of Alzheimer's Disease – Retina

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Short Communication

Preface

Alzheimer's disease is characterized by a pathological accumulation of Amyloid Beta (Aβ) protein accompanied by hyper-phosphorylation of tau protein with a consequent neuronal degeneration and decimation of cognitive cerebral functions. Alzheimer's disease as a frequent neurodegenerative condition of the geriatric population demonstrates an estimated prevalence of 36.5 million in the Western world. Alzheimer's disease chiefly affects the brain although retina is often incriminated and typically displays a significant impairment of retinal neurovascular coupling. Degenerative alterations within the retinal ganglion incumbent to Alzheimer's disease can be appropriately analyzed in order to categorize the incipient neurodegenerative process. As neuronal modifications are predominant in Alzheimer's disease and mild cognitive impairment, cogent neuropathology and neuroimaging investigations can be beneficially employed to depict alterations arising within the adjacent, associated cerebral microvasculature [1,2].

Mild cognitive impairment depicts an enhanced probable emergence of Alzheimer's disease. Thus, adequate clinical characterization of the disease is crucial with the enunciation of contemporary diagnostic parameters which indicate the transition of mild cognitive impairment to full blown Alzheimer's disease. Alzheimer's disease is accompanied by minimizing of blood circulation within the deep-seated vascular plexus. Specific criterion of evaluating retinal vasculature can deliver significant information and provide beneficial biomarkers for assessing the preliminary or final diagnosis, monitoring transition of mild cognitive impairment to Alzheimer's disease or to predict disease progression [1,2].

Disease characteristics

Vascular alterations, as an intrinsic component or a coexistent pathology, can interrelate with pathogenic manifestations of Alzheimer's disease such as neurodegeneration along with cognitive impairment in order to constitute the "vascular cognitive impairment" manifestation. Pathological symptoms of the implicated vasculature are enunciated in around three fourths (75%) subjects with dementia. Vascular alterations are comprised of White Matter Hyper-intensities (WMHs) which appear on account of chronic ischemia of the sub cortical region with incrimination of miniature blood vessels, infarcts within vessels of higher calibre, appearance of lacunar infarcts as in the thalamus, coexistent arteriosclerosis and atherosclerosis and proportionate instances of Cerebral Amyloid Angiopathy (CAA) [2,3]. Intravascular deposition of Amyloid Beta (Aβ) within the vessel wall is exemplified as cerebral amyloid angiopathy, a process which is accompanied by micro-hemorrhages and micro-infarcts. CAA demonstrates an incidence of roughly 20% to 40% within the non-demented elderly and approximately 50% to 60% in the demented geriatric population. Alzheimer's disease is intensely concurrent with cerebral amyloid angiopathy and can be discerned in a majority (85% to 95%) instances [2,3].

Disease pathogenesis

Declining cerebral blood flow and relevant modifications of the blood-brain barrier are incriminated in the pathophysiology of Alzheimer's disease in association with a probable inopportune clearance of Amyloid Beta (Aβ) protein. Retina is contemplated as a pertinent generator of vascular biomarkers which can indicate the emergence of Alzheimer's disease. Retinal vasculature can be subjected to noninvasive imaging at miniature, micro-meter levels with various imaging modalities such as fund us photography, assessment of choroidal thickness with Enhanced Depth Imaging Optical Coherence Tomography (EDI-OCT) and Optical Coherence Tomography Angiography (OCTA) [3,4]. Alzheimer's disease is a complex disorder and enunciates multifactorial aetiologies. Several factors are implicated in disease pathogenesis and progression and preliminary factors significantly contribute to a continuum of the deteriorative process. Aberrant, entangled Amyloid Beta (Aβ) protein filaments and hyper-phosphorylated tau protein are aggregated into

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cogent neurofibrillary tangles. Accumulation of aforesaid debris can initiate a cascade of secondary manifestations such as inflammation, oxidative stress, vascular abnormalities or neuronal decimation. Disorganized miniature vascular structures of the brain are incumbent in the pathological evolution of Alzheimer's disease and mild cognitive impairment. Aforesaid neurodegenerative conditions are accompanied by preliminary neurovascular dysfunction and a consequently dysregulated vascular flow which contributes to disease pathogenesis. Assessment of vascular density of peripheral ring of the macula along with cogent scoring of white matter hyper-intensities can be achieved with magnetic resonance imaging in Alzheimer's disease [3,4]. Functional modifications appear as a preliminary reaction and commonly precede decimation of retinal neurons.

Proportion of Amyloid Beta (Aβ) protein exemplified in cerebrospinal fluid is concordant to degree of arterial dilatation. Elevated levels of amyloid beta in the cerebrospinal fluid are concurrent with superior neurovascular coupling. Percentage of vascular amyloid beta in combination with neurofibrillary morphological abnormalities are inversely concordant with Amyloid Beta (Aβ) and directly interrelated to phosphorylated- tau protein values within the cerebrospinal fluid. Thus, marked protein accumulation in the brain and retina can directly influence neurovascular coupling [4,5].

Confirmed instances of Alzheimer's disease can be denominated with specific biomarkers such as amyloid deposits discerned on Positron Emission Tomography (PET) scan. Additionally, Fractal Dimension of arteriolar network (FDa), Central Retinal Vein Equivalent (CRVE), Central Retinal Artery Equivalent (CRAE), fractal dimension of venular network, Curvature Tortuosity of arterioles (cTORTa), choroidal thickness, vessel density, Foveolar a Vascular Zone (FAZ) and curvature tortuosity of venules can be assessed in Alzheimer's disease. Instances of primary vascular aetiology or the concurrence of a vascular co-pathology instead of features of Alzheimer's disease require demarcation. Alzheimer's disease contingent to amyloid deposition can depict alterations as detected with clinical, neuroimaging and fluid-based biomarkers. Variable choroidal thinning is cogitated on Enhanced Depth Imaging Optical Coherence Tomography (EDI-OCT) [4,5]. Optical Coherence Tomography Angiography (OCTA) employed for assessing dimensions of vascular density in amyloid-deposited Alzheimer's disease or within the Foveolar a Vascular Zone (FAZ) is identical in preclinical and clinical disease.

Tortuosity of venules is inversely concurrent with scoring of white matter hyper-intensities as discerned with Magnetic Resonance Imaging (MRI). Inverse correlation of macular vessel density and white matter hyper-intensities score in Alzheimer's disease can indicate modifications within the microvasculature as cogitated in chronic cerebral micro-infarctions. However, concurrence of parameters of retinal vascular assessment to indicative biomarkers of cerebrovascular fluid or Mini-Mental State Examination (MMSE) is lacking [5,6].

Clinical elucidation

A transitional phase of variable duration precedes the clinical emergence of symptomatic Alzheimer's disease. Implicated geriatric individuals display a heterogeneous cognitive and functional impairment usually defined as beneath the symptomatic threshold of dementia. Aforesaid manifestation is denominated as "mild cognitive impairment" where incriminated subjects demonstrate an enhanced possible emergence of dementia, particularly Alzheimer's disease.

Figure 1: Alzheimer's disease - modifications of cerebral vessels is concordant with modifications of retinal vessels.

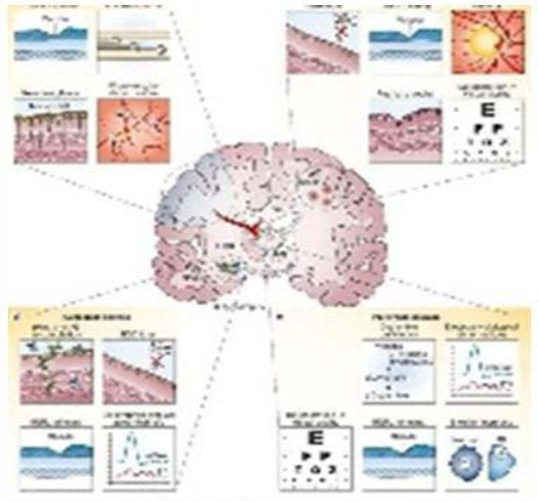

Figure 2: Alzheimer's disease demonstrating variable pathogenesis with accumulation of amyloid beta and tau proteins.

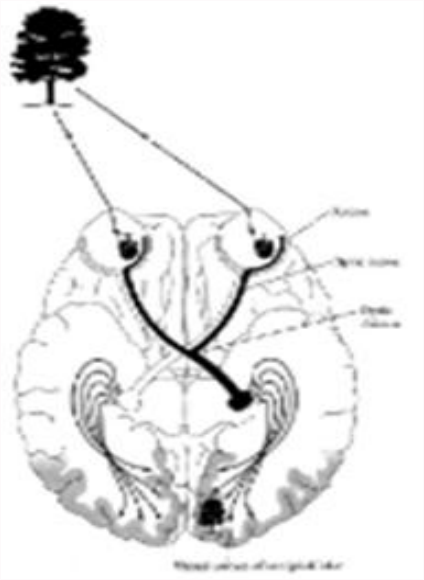

Figure 3: Alzheimer's disease with retinal vasculature mimicking the alterations of cerebral arteries.

The dementia characteristically depicts a severe decline of cognitive functions with ensuing socio-behavioral manifestations. Individuals with Alzheimer's disease can delineate symptoms such as visual impairment, narrowed visual field, dyschromatopsia, deficiency in contrast sensitivity, aberrant eye motility and modifications of visual-

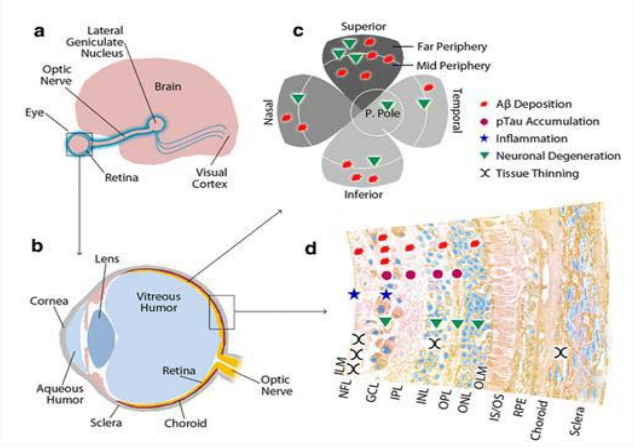

Figure 4: Alzheimer's disease depicting various mechanisms of generation with amyloid, p-tau, neuronal loss and inflammation.

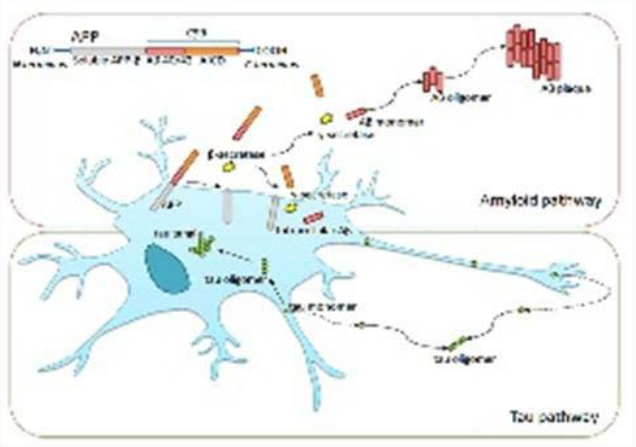

Figure 5: Alzheimer's disease with enunciation of amyloid pathway and tau pathway in disease pathogenesis.

evoked potentials [5,6].

Histological elucidation

Alzheimer's disease demonstrates a decline in quantification of retinal ganglion cells and associated axons within the retinal nerve fiber layer. Reduction of retinal ganglion cells are contingent to occurrence of extracellular plaques and accompanying intracellular deposition of Amyloid Beta (Aβ) as enunciated within the retina of individuals with Alzheimer's disease. Ganglion cell layer is attenuated within central and temporal regions in Alzheimer's disease as discerned with Optical Coherence Tomography (OCT). Centric zone of the retina within the dimension of 0 mm to 2 mm is majorly (97%) composed of neurons and residual (3%) is constituted by displaced amacrine cells. Alzheimer's disease maximally implicates the segment of retinal ganglion cells, designated as M-cells, which are principally aggregated within the temporal macula [1,2].

Amyloid Beta (Aβ) protein is aggregated within and surrounding the cerebral blood vessels, the circulation of which is challenging to investigate *in vivo*. Thus, evaluation of retinal micro-vasculature as a determinant of Alzheimer's disease is adopted although assessment of disease progression is limited. Retinal vessels can be considered as surrogate indicators of cerebral microcirculation, thus histological elucidation and imaging studies are beneficial.

Functional reaction of retinal vessels, as a component of cognitive impairment, is observed in Alzheimer's disease and mild cognitive impairment. Investigation with Dynamic Vessel Analyzer (DVA) demonstrates a characteristic response curve to flicker light impulse on account of primary vasodilation and secondary vasoconstriction, as exemplified in the aforesaid disorders. Vasodilation occurs as a consequence of stimulation of photoreceptors with a subsequently enhanced retinal blood circulation. The process which mediates aforementioned vascular response is denominated as "neurovascular coupling" [1,2]. Representation and amplitude of the typical biphasic response can categorically indicate the quality of auto-regulation. Comprehensive reduction of vessel response can significantly impact arterial vasodilation. As cerebral and retinal micro-circulation is reduced in Alzheimer's disease, chronic hypo-perfusion can impair endothelial function along with production of nitric acid, which is critical for vasodilation. Declining vascular response arises on account of enhanced rigidity of retinal arteries and cerebral vasculature in Alzheimer's disease in addition to a characteristically thickened basement membrane. Diminishing vascular response can also be secondary to neuronal degeneration with a consequently decreased metabolic requirement [5,6] (Figures 1-5).

Investigative Assay

Although miniature cerebral vessel disease is incriminated in the generation of Alzheimer's disease and mild cognitive impairment, assessment of cerebral microcirculation is a challenging task. Cerebral and retinal vasculature is identical in embryology, origin anatomical and physiological properties. Thus, evaluation of retinal vessels can provide insights into the generation of Alzheimer's disease and mild cognitive impairment. Functional and morphological characteristics of retinal vessels are contemplated as cogent indicators of disease progression. Decisive descriptions are contingent to fund us photography and contemporary techniques which permit pertinent, topographic, qualitative assay and quantitative assessment of magnitude of retinal vessels at varying levels of depth- resolution. Microvascular networks of retina, as discerned with uninvolved and disease-specific state, can be assayed with devices such as Dynamic Vessel Analyzer (DVA) and Optical Coherence Tomography Angiography (OCTA). However, evaluation of extensive functional and morphological characteristics of macular microvasculature in Alzheimer's disease and mild cognitive impairment is currently lacking [6,7]. Optical Coherence Tomography Angiography (OCTA) delineates adequate morphological characterization of retinal and anterior choroidal blood vessels in the absence of a dye. Employment of OCTA demonstrates a superior depth resolution, superlative visualization of deep-seated vascular layers besides an amplified vascular elucidation of diverse ocular and systemic disorders. A competent Magnetic Resonance Imaging (MRI) can be contemplated as a contemporary biomarker is discerning vascular alterations characteristic of Alzheimer's disease. Vascular alterations can also be assessed with recently elucidated biomarkers which can complement the currently applicable system designated as Amyloid (A), Tau (T) and Neurodegeneration (N) or the ATN system [6,7]. Retinal vascular alterations of Alzheimer's disease, as described with fund us photography, comprise of enhanced venous diameter, reduced arterial diameter and a decline in the fractional dimension. Additionally, choroidal thinning enhanced Foveolar Avascular Zone (FAZ) with a declining vessel density and blood flow is cogitated in clinical and preclinical Alzheimer's disease.

Ophthalmological enunciation of associated, usually asymptomatic co-morbid conditions can impact retinal vascular magnitude. Thus, a comprehensive ophthalmological screening is recommended. Evaluation of retinal biomarkers in categorical instances of Alzheimer's disease exemplify as cortical atrophy and occurrence of amyloid and tau protein in the cerebrospinal fluid. Also, application of amyloid Positron Emission Tomography (PET) scan can endorse the clinical diagnosis and permit comparison of contemporary biomarkers to existing "gold standards" [7,8]. Non invasive retinal vascular biomarkers for assaying Alzheimer's disease are constituted by enhanced Central Retinal Artery Equivalent (CRAE), reduced Central Retinal Vein Equivalent (CRVE), diminished fractal dimension, minimal choroidal thickness, minimized vessel density and augmented Foveolar a Vascular Zone (FAZ). Interrelation of retinal vascular parameters with white matter hyper-intensities can also be examined with magnetic resonance imaging. Retinal vascular parameters are evaluated by fund us photography, EDI-OCT and OCTA. Subjects undergo a concurrent, standardized screening comprising of a comprehensive medical history, neuropsychological examination, assessment of Apolipoprotein E ε4/ε4 (APOE ε4/ε4) genotype, blood pressure, neuroimaging and lumbar puncture for examining the cerebrospinal fluid [7,8]. Magnetic Resonance Imaging (MRI) can be visually scored for atrophic changes as cogitated upon T1-weighted images and are denominated as medial temporal lobe atrophy, global cortical atrophy and parietal cortical atrophy. Assessment of retinal vasculature in concurrence with white matter hyper-intensities, lacunar infarcts and micro-bleeds can be discerned.

Evaluation of cerebrospinal fluid with Enzyme Linked Immunosorbent Assay (ELISA) for the detection of amyloid beta 1-42 (Aβ1-42), tau 181 and phosphorylated Tau (pTau) can be achieved. The proportion of tau 181 to amyloid beta 1-42 commonly exceeds ≥ 0.52 in definitive Alzheimer's disease [1,2].

Positron Emission Analysis (PET) scan for vascular deposition of amyloid can be assessed with cogent tracers and visually interpreted as amyloid reactive or amyloid non reactive.

Ophthalmological assessment is required for screening and a subsequent correction of visual acuity, assay of intraocular pressure and slit lamp examination of anterior and posterior segment. Occurrence of specific diseases mandate an exclusion from examination such as severe cataract, age-specific macular degeneration, glaucoma and diabetes mellitus [8,9].

Vascular imaging of the retina can be achieved with fund us photography, Enhanced Depth Imaging Optical Coherence Tomography (EDI-OCT) and Optical Coherence Tomography Angiography (OCTA). Central Retinal Artery Equivalent (CRAE), Central Retinal Vein Equivalent (CRVE), arteriole-to-venule ratio, Fractal Dimensions of arteriolar network (FDa), fractal dimension of venular network, curvature Tortuosity of arterioles (cTORTa) and curvature tortuosity of venules necessitate an appropriate assessment [8,9].

References

1. Querques G, Borrelli E, Sacconi R, De Vitis L, Leocani L, Santangelo R, et al. Functional and morphological changes of the retinal vessels in Alzheimer's disease and mild cognitive impairment. Sci Rep. 2019;9(1):63.
2. Haan JD, van de Kreeke JA, van Berckel BN, Barkhof F, Teunissen CE, Scheltens, et al. Is retinal vasculature a biomarker in amyloid proven Alzheimer's disease? Alzheimer's Dementia (Amst) 2019:11;383-91.
3. Snyder HM, Corriveau RA, Craft S, Faber JE, Greenberg SM, Knopman D, et al. Vascular contributions to cognitive impairment and dementia including Alzheimer's disease. Alzheimers Dement. 2015;11(6):710-7.
4. Serrano-Pozo A, Muzikansky A, Gómez-Isla T, Growdon JH, Betensky RA, Frosch MP, et al. Differential relationships of reactive astrocytes and microglia to fibrillary amyloid deposits in Alzheimer disease. J Neuropathol Exp Neurol. 2013;72(6):462-71.
5. Sweeney MD, Sagare AP, Zlokovic BV. Cerebrospinal fluid biomarkers of neurovascular dysfunction in mild dementia in Alzheimer disease. J Cereb Blood Flow Metab. 2015;35(7):1055-68.
6. Arvanitakis Z, Capuano AW, Leurgans SE, Bennett DA, Schneider JA. Relation of cerebral blood vessel disease to Alzheimer's disease dementia and cognitive function in elderly people: A cross sectional study. Lancet Neurol. 2016;15(9):934-43.
7. Coscas G, Lupidi M, Coscas F. Heidelberg Spectralis Optical Coherence Tomography Angiography: Technical Aspects. Dev Ophthalmol. 2016;56:1-5.
8. Kwon JY, Yang JH, Han JS, Kim DG. Analysis of retinal nerve fibre layer thickness in Alzheimer disease and mild cognitive impairment. Korean J Ophthalmol. 2017;31(6):548-56.
9. Cunha LP, Almeida AL, Costa-Cunha LV, Costa CF, Monteiro ML. The role of optical coherence tomography in Alzheimer's disease. Int J Retina Vitreous. 2016;2:24.