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"β-Amyloid, the Central Player in Alzheimer's Disease Neurodegeneration, may be a Fulcrum in Glaucomatous Pathogenesis also"

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Abstract: Glaucoma is suggested to be related to Alzheimer's disease (AD) as both diseases involve neurodegeneration but this connection needs to be concretized by more evidences. β-amyloid is known to play significant role in neurodegenerative process of AD and this has been indicated by many *in vitro*, *in vivo* and computational studies, many of which have been mentioned in the present review. There is a huge possibility that β-amyloid is also involved in pathogenesis of glaucoma. Evidences in this regard are quite few. The present review emphasizes the importance of searching the connection between AD and glaucoma to enhance our understanding of glaucoma in a better way.

Keywords: β-Amyloid, Alzheimer's disease, Glaucoma, Neurodegeneration

Running title: Importance of β-Amyloid in Alzheimer's disease and Glaucoma.

Introduction: β-amyloid is a major player in neurodegenerative process of AD. Since AD and glaucoma have been found to be related in many aspects, the possibility of β-amyloid playing a significant role in glaucoma pathogenesis is also fairly high. Role of β-amyloid in AD neurodegeneration, connection between glaucoma and AD have been described in the following sections.

Role of β-Amyloid in Neurodegenerative process of AD:

Over a period of time, a large body of evidence has developed that indicates towards primary role of β-amyloid protein fragments in the neurodegenerative process. A series of biochemical events starts that finally leads to death of neuronal cells. These events involve a number of alterations that occur in the cells' physiology [1]. For instance, there is imbalance of intracellular calcium homeostasis by activation of calcium channels, intracellular calcium stores and subsequent formation of free radicals by calcium sensitive enzymes [2]. Secondary processes such as inflammation produce more free radicals and lead to apoptotic induction [2]. The aggregation and deposition of β-amyloid having 40-42 residues leads to formation of stable and ordered fibrils and small, soluble and cytotoxic oligomers [3]. The toxicity of the oligomers is attributed to their ability to bind to the vertebrate lipid membranes through GM1 ganglioside receptors and to affect their integrity [3]. The surfaces of the membranes promote conversion of

amyloid forming proteins in to amyloidogenic proteins and toxic aggregates that reduce the integrity of the membranes [4]. This has been demonstrated in artificial model membranes where close similarity has been observed between the mechanism of membrane permeabilization of proteins that form amyloid to that of anti-microbial peptides and pore forming toxins [4]. Contribution of the two amyloid peptides having 40 and 42 amino acid residues is differential towards the disease process, where the 42 amino acid residue containing β-amyloid ($A\beta_{42}$) appears to be more toxic than the one that has 40 residues ($A\beta_{40}$) [5]. Even minor changes in the $A\beta_{42}$: $A\beta_{40}$ ratio bring about alteration in the morphology of the amyloid fibrils, aggregation kinetics and synaptic functions tested in both *in vivo* and *in vitro* [5]. Further, it has been demonstrated in pyramidal neurons of rats organotypic slices, that naturally secreted dimers and trimers of β-amyloid induce loss of hippocampal synapses but monomers do not have such an effect [6]. Apoptosis and interference in axonal transport, the two interdependent mechanisms may be considered responsible for neuronal damage due to insolubility of proteins [7]. Thus, insolubility of proteins has been hypothesized to cause neurodegeneration however, it is fairly possible that amyloid precipitation may be occurring after its soluble form has already done the neuronal damage [7].

Cleary et al. (2005) had also demonstrated that soluble oligomers of β-amyloid together with dimers and trimers are needed and are sufficient also to cause rapid destruction of learned behavior as they can impair cognitive function leading to dementia in AD [8]. Another evidence of involvement of soluble β-amyloid derived oligomers in memory loss occurring in AD came from the study done by Lacor et al. (2007) which showed that the β-amyloid derived oligomers bring about synaptic damage [9]. Shankar et al. (2009) extracted the soluble β-amyloid derived oligomers from the cerebral cortex of AD patients directly suggesting that these oligomers inhibited long term potentiation while increased long term depression [10]. They also suggested that these soluble oligomers decreased the dendritic spine density in hippocampus of normal rodents and also destroyed the memory of learned behavior in normal rats [10]. Walsh et al. (2002) had reported that generation of β-amyloid oligomers occurs soon after formation of the peptide in specific intracellular vesicles followed by their secretion from the cells. Marked inhibition of the hippocampal long term potentiation was observed in rats upon injecting the cerebrum of rats with medium containing these oligomers and β-amyloid monomers but not amyloid fibrils [11].

Bioinformatics based evidences for β-Amyloid's role in AD

Amyloids are insoluble long fibers and their atomic level structural resolution has proved to be difficult. Their tendency to aggregate makes their structural characterization difficult [12]. Due to this, computational methods have been preferred so as to develop their models, deduce their chemical behavior and to check their stabilities, with validations done using targeted experiments [13]. Considering the bioinformatics based studies done for β-amyloid, a few hundred of them come in to picture. A total of 1455 results were returned on the PubMed (NCBI) website upon searching "*Bioinformatics, Beta amyloid protein*" (Date of searching: 24th April 2022). The

number of results reduced to 1034 upon searching "*Bioinformatics, Beta amyloid protein, Alzheimer's disease*" indicating that more than half of the bioinformatics based studies for β-amyloid protein have been done in relation to AD (Date of searching: 24th April 2022). The bioinformatics data available for β-amyloid protein in relation to AD shows a number of significant aspects of the protein. For instance, as early as in the year 1999, George and Howlett reported computationally derived models for β-amyloid protein and its possible interactions. Their proposed models were not only consistent with experimental structural data, they were also used in studying other relevant aspects of β-amyloid like- explanation of increased fibrillogenic nature of dutch family mutation of β-amyloid, examination of possible docking interactions of anti-aggregation inhibitors (IDOX) with β-amyloid [14]. Further, computational and experimental studies done by Guo et al. (2004) resulted in structural models for the core of β-amyloid protein fibrils that could serve as the building block of β-amyloid (1-40) fibrils [15]. Soreghan et al. (2005) used proteomics approach combined with network analyses to elucidate the effect of oxidation of synaptic protein in PS1+AbetaPP mice model for AD and showed that three pathways get altered by it namely- (a) iNOS-integrin signaling pathway, (b) rab-lyst vesicular trafficking and (c) CRE/CBP transcription regulation [16]. They further concluded that their results could help in establishing an initial database for AD having oxidatively modified proteins [16]. Dickerson et al. (2005) used computational docking models and experimental screening to identify five compounds that could completely inhibit the amyloidogenic effect of AChE [17]. Chen et al. (2006) developed a computational method for ranking and ordering AD related proteins using protein interaction network data for AD [18]. Study done by Wang et al. (2008), that used the GNNQQNY crystal structure and high temperature molecular dynamics simulation, helped to understand the fibril aggregation pathways [19]. Ye et al. (2013) applied molecular dynamics simulations on many amyloidogenic protein systems suggesting further that these simulations could be used to understand the mechanism of aggregation of amyloid and to design inhibitors for it [20]. Another computational study done by Jang and Shin (2008) using REMD simulation for β-amyloid (10-35) dimers, trimers and tetramers showed as the size of oligomer increases, the number of possible configuration decreases. Also, there are multiple pathways of aggregation process responsible for the structural diversities of the β-amyloid [21]. To centralize the bioinformatics data related to all the amyloid proteins and their precursors, Pawlicki et al. (2008) created a free online database named AMYPdb that integrated 31 families, with 1705 proteins from 600 organisms and reported highly specific patterns for each of the amyloid families along with those which may be involved in protein aggregation and misfolding [22].

Attempts have been made in order to select inhibitors of β-amyloid aggregation using computational methods by Chen et al. (2009) where they aimed to identify compounds with small molecular weights that were similar in activity to β-sheet breaker pentapeptides, which could alleviate AD symptoms but have low efficacy due to their large size, instability and inability to penetrate membranes efficiently [23]. Combinational study involving molecular dynamics, bioinformatics and density functional theory has been done in order to elucidate the

processes like hydrolytic breakdown of Ala-Thr and Val-Ile peptide bonds of APP by intra-membrane aspartyl protease presenilin 1 (PS1). On the basis of the results obtained for analyses of these processes involved in the formation of 40-42 amino acids long β-amyloid protein, it was suggested that generation of β-amyloid with 40 amino acids is more favorable and it is formed about nine times more in amount than β-amyloid with 42 amino acid residues [24].

Role of β-Amyloid in Neurodegenerative process of glaucoma:

β-amyloid and tau protein are found to be deposited in the retina and aqueous humor in both AD and glaucoma [25]. This indicates that β-amyloid may be involved in glaucomatous process just as in AD. A recent review done by Inyushin et al., (2019) also suggests that β-amyloid peptides accumulate and play important role in glaucoma in addition to AD [26]. They further evidenced for a common systemic source of β-amyloid for both diseases, which accumulates in and damages tissues during progress of these disorders along with indicating its relation to platelets [26]. Effect of intravitreal β-amyloid (1-42) has been studied on optic nerve and retinal morphology in animal models and that of intravitreal β-amyloid (1-40) has also been studied and they have been found to be deteriorating in both cases in time and dose related manner [27]. Studies done by Ito et al., (2012) and Yan et al., (2017) in monkey models and many others have suggested that increase in intra-ocular pressure causes upregulation of β-amyloid (1-42) in different regions of eye like retina, optic nerve head etc. [28, 29]. Tsuruma et al., (2010) had suggested on the basis of their study that regulation of β-amyloid can be seen as a new therapeutic target for glaucoma, especially in patients having AD [30]. All these experimental evidence based studies indicate that β-amyloid is associated with glaucoma but how it is involved in the progress of this disease is not clear yet.

Bioinformatics based evidences for β-Amyloid's role in Glaucoma

It is a matter of surprise that only 2 results were returned on the PubMed (NCBI) website upon searching "*Bioinformatics, Beta amyloid protein, glaucoma*" (Date of searching: 24th April 2022). This shows that very less research has been done in the field of glaucoma in relation to its connection with β-amyloid. One of these works involved a genome-wide association study (GWAS) of African ancestry populations along with evaluation of potential mechanisms of pathogenesis with POAG [31]. In this study, variants at APBB2 locus (Amyloid beta precursor protein binding family member 2) exhibited differential association with POAG by ancestry [31]. The other simulation based study done by Wang et al., (2018) demonstrated the capability of DMD/PRIME20 simulations to predict peptide amyloidogenicity and fibril structure [32].

The β-amyloid connection between AD and glaucoma

Glaucoma is a well-known multifactorial neuro-degenerative disease hallmarked by death of RGCs [33] that leads to irreversible vision loss [34]. Many epidemiological and histological overlaps are there in AD and glaucoma pathogenesis but some missing links also exist that need more evidences [c]. Both glaucoma and AD are slow age related neuro-degenerative disorders.

This is the reason why some researchers consider glaucoma to be ocular AD [35]. Glaucoma can be kept in the group of neurodegenerative diseases as many evidences have come up to support this notion. Epidemiological studies done by Tamura et al. (2006) revealed a higher frequency of open angle glaucoma in AD patients [36]. There have been a number of studies that have shown association of a higher frequency of glaucoma with AD [37-39]. The study done by Tamura et al. (2006) has reported 2.5 times higher percentage of AD patients that have glaucoma as compared to the normal patients [36]. Many studies show that AD patients exhibit RGCs' loss that is a typical feature of glaucoma along with optic neuropathy and visual function impairment [40-43]. Conversely, Helmer et al. (2013) have reported a higher possibility of AD in glaucoma patients [44]. Also, an earlier study done by Bayer et al. (2002) revealed association of glaucoma with AD as well as PD [45]. Gupta et al. (2007 and 2008) have reported presence of neurodegenerative lesions in the intracranial optic nerve, visual cortex and geniculate nucleus [46, 47]. In this optic neuropathy, deposition of β-amyloid [48-50] and γ-synuclein [51] have been found to occur in the retina. β-amyloid is also found to be responsible for the apoptosis of RGCs along with corresponding decreased level of the protein in vitreous humor in glaucoma patients [52]. Further presence of abnormal Tau (AT8) and pTau (phosphorylated Tau) have been confirmed in human ocular tissue with uncontrolled intra-ocular pressure and in donated glaucomatous eyes [47, 53]. Recently, Yan et al. (2017) have reported for the first time, the hallmark AD like pathologies such as β-amyloid 1-42 and tau depositions, in the lateral geniculate nuclei of rhesus monkeys with chronic glaucoma established using laser photocoagulation [29]. The group has also reported an association of the loss of considerable portions of the visual field in glaucomatous condition in human with pathologies of the visual centers in the brain and these are very much similar to the features seen in neurodegenerative disorders [29] like AD.

Thinning of the retinal nerve fiber layer occurs in both glaucoma [54] and AD [55], which strongly backs the notion of mechanistic similarity between the two pathologies. The lateral geniculate nuclei are also affected in both diseases. In glaucoma, the magnocellular tissue of the lateral geniculate nuclei is lost significantly [56], while in AD, the significant a deposition of the AD biomarkers like Tau, β-amyloid, APP proteins and inflammation have been reported [57]. Both these diseases are characterized by early onset of alterations in the neuronal circuitry process and phosphorylation of MAPK which are further followed by inflammation, glial reaction, reactive oxygen species production, mitochondrial abnormalities and propagation of the neuro-degenerative process and cell death [58]. Both exhibit synaptic dysfunction and neuronal death in the retina [59, 60]. Many members of the heat shock proteins are involved in both neurodegenerative disorders and glaucoma [61]. Also, glaucoma shares its neuro-inflammatory patho-mechanism with AD and PD with one of the common links being activation of microglial cells [62]. This activation is caused by the protein aggregates such as pTau, β-amyloid, synucleins that trigger infiltration of the peripheral immune cells in to the CNS that activate resident microglia on a large scale [62].

Considering the role of β-amyloid in AD, it is known that β-amyloid initially occurs in monomeric, oligomeric and fibrillary forms [63] which aggregate to form oligomers and protofibrils and amyloid fibrils in a concentration dependent way. The β-amyloid peptides formed by 36-43 amino acids are toxic with the 42 amino acid peptide being the most neurotoxic amyloidogenic fragment which is the main component of the senile plaques. Shankar et al. (2008) have reported that β-amyloid oligomeric extracts from cerebral cortex of AD patients [64] can adversely affect memory and learning by inhibiting long term synaptic plasticity occurring as long term potentiation through phosphorylation of p38 MAPK [65], representing the early stages of AD progression. Elevation in the concentration of β-amyloid also affects synaptic transmission and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid current [66]. In a similar way in glaucoma, increased level of soluble β-amyloid in retina may impair the synaptic circuitry and retrograde trafficking of the neuro-trophic factors in ON axons [67]. This elevation in the concentration of β-amyloid in case of glaucoma may be induced by the high intra-ocular pressure [48]. Moreover, APP is also reported to be expressed in HTM tissue [68] giving rise to the possibility for β-amyloid production in HTM cells also. Thus, in glaucoma progression also, β-amyloid induced by high IOP may be contributing to synaptic progressive dysfunction in the retina and lead to impairment of vision [48].

Hence, a number of studies have shown association of glaucoma with AD, with involvement of β-amyloid protein in one way or the other. All these evidences give considerable support to the possibility of a strong connection between glaucoma and AD, however some others have demonstrated conflicting results regarding frequency of AD in glaucoma patients [69, 70]. There have been many instances where deposition of β-amyloid and tau have been reported in the retina of glaucoma patients but the pathogenic relation between glaucoma and AD is still elusive. Very few evidences have been at the pathogenic level where glaucoma and AD have common features. So it is quite clear that the possibilities of involvement of β-amyloid protein in causation and progress of various forms of glaucoma are fairly high. To get more concrete evidence for establishment of relatedness between glaucoma and AD, studies involving elucidation of mode of action, function, behavior, other activities and interactions of β-amyloid with other proteins in reference to both glaucoma and AD are needed.

Conclusion: Evidences to establish the role of β-amyloid in glaucoma are very few in comparison to that for AD. Since both these diseases are related, the possibility of important role of β-amyloid in glaucoma is also high and this aspect of glaucoma pathogenesis should be searched to enhance our understanding of glaucoma.

Clinical Significance: This review emphasizes the importance of studies involving elucidation of role of β-amyloid in glaucoma. These will not only help in understanding both AD and glaucoma in a better way but will also help in elucidating their patho-mechanisms, their relation with each other and possibly indicate their therapeutics.

Abbreviations: Acetylcholinesterase (AChE), Alzheimer's Disease (AD), Amyloid precursor protein (APP), Brain Derived Neurotrophic Factor (BDNF), Human trabecular meshwork (HTM), Intraocular Pressure (IOP), Matrix Metalloproteinase2 (MMP2), Parkinson's Disease (PD), Primary Open Angle Glaucoma (POAG), Replica Exchange Molecular Dynamics (REMD), Retinal ganglion cells (RGCs), Retinal Pigment Epithelium (RPE), TANK-binding kinase 1 (TBK1), Tissue Inhibitor of Metalloproteinase 3 (TIMP3).

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