Alzheimer’s Disease-Related Amyloidopathy in Visual Impairment

Can Zhang*

Genetics and Aging Research Unit, Mass General Institute for Neurodegenerative Diseases (MIND), Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, 02129-2060, USA

Abstract

Alzheimer’s disease (AD) is a devastating neurodegenerative disease and the primary cause of dementia, with no cure available. The pathogenesis of AD is believed to be primarily driven by the accumulation of Aβ, a 4-kDa peptide generated from the amyloid-β precursor protein (APP) through proteolysis. APP is a type-I trans-membrane protein which is constitutively expressed in many tissues, including the eye. Emerging evidence support that visual impairment and several common eye disorders may share common pathogenic determinants with AD. Over the past decade, an increasing number of researches have been utilizing mouse models to investigate the underlying mechanisms of human disorders. Intriguingly, AD animal models present devastating amyloidopathy not only in the brain but also in the eye. This article aims to describe the progress in understanding the pathophysiology and pathogenesis of AD, focusing on the amyloidopathy in visual impairment. Moreover, the studies described in this review support the potential use of non-invasive ocular tests for screening AD patients at an earlier stage and for assessing treatment efficacy of AD.

Keywords: Alzheimer’s disease; Amyloid-β; Amyloidopathy, Amyloid-β precursor protein; Tau; Visual impairment; Retina; Lens; Animal model

Introduction

AD is a devastating neurodegenerative disease and is the primary cause of dementia. Amyloidopathy and tauopathy underlie the two pathological hallmarks in the AD brain [1-4]. Recently, many reports described that visual disturbance occurs in AD patients, which might be affected by amyloidopathy [5-7]. Interestingly, considerable studies using AD animal models demonstrate devastating amyloidopathy not only in the brain but also in the eye, supporting the role of amyloidopathy in the pathology of visual impairment. This study aims to describe the progress that has been made in understanding the pathophysiology and pathogenesis of AD, focusing on the amyloidopathy in the visual impairment. We will discuss the background of AD, the visual changes in AD patients and the involvement of amyloidopathy in several common eye disorders. And then we will discuss the findings of amyloidopathy in the eye of AD mouse models.

Basics of Alzheimer’s Disease (AD)

The primary clinical features of AD are characterized by deterioration of memory and cognitive function, progressive impairment of activities of daily living, and several neuropsychiatric symptoms [1]. On the cell and molecular levels, the pathophysiology of AD is characterized by two distinctive features: amyloid plaques comprised primarily of a small peptide named Aβ [2-4], and neurofibrillary tangles composed of hyperphosphorylated tau. While Aβ42 and Aβ40 are the two primary Aβ species, Aβ42 is more prevalent than Aβ40 in amyloid plaques. Considerable evidence from genetics, biochemistry and molecular biology supports the "amyloid-cascade hypothesis" which states that the production and excessive accumulation of Aβ is the primary pathological event leading to AD [2,8]. Specifically, accumulation and aggregation of Aβ can induce a series of toxicity-mediated "gain-of-functional" activities including inflammatory responses, followed by hyperphosphorylation of the tau protein, formation of fibrillary tangles, and activation of apoptotic pathways [2-4]. In parallel, these gained and often toxic activities contribute to "loss-of-functional" activities in the proteasome and the lysosome, as well as the mitochondria [3,9-12]. Ultimately, these abnormal functional activities lead to neuronal dysfunction and cell death [3,9-12].

Aβ is produced via a sequential cleavage of amyloid-β precursor protein (APP) by β-secretase (BACE1) and γ-secretase [Figure 1] [3,13-16]. APP is a type-I trans-membrane protein that is constitutively expressed in many tissues. The initial cleavage of APP can occur through α- or β-secretase. α-Secretase cleavage produces sAPPα and the α-C-terminal fragment [α-CTF or C83]; β-secretase cleavage produces sAPPβ and β-C-terminal fragment (β-CTF or C99). Following trophic factor deprivation, sAPPβ can be further cleaved by an unidentified protease to produce N-APP, which contains the N-terminal 286 amino acids of APP [17,18], C83 and C99 can be further cleaved by γ-secretase to produce P3 or Aβ.

One of the strongest support of the “amyloid hypothesis” in AD is based on genetic studies. AD is a genetically complex disorder. Based on the age of onset, it has two primary forms: early or late-onset AD. More than 200 fully penetrant mutations in the amyloid β-protein precursor [APP], presenilin 1 (or PSEN1), and presenilin 2 (PSEN2) have been identified for early-onset familial AD (FAD) (<60 years old; 5-10%
cases) [3,8,19], whereas 90-95% cases are late-onset AD (>65 years old) and a variant (e4) of the gene encoding apolipoprotein E (APOE) has been associated with this disease type [20]. To date approximately 80% of the late-onset AD genetic variance still remains elusive [21]. Recently several genome-wide association studies have identified several novel AD candidate genes [3,22]. Functional characterization of these AD candidate genes has confirmed the important pathogenic factors of AD, including amyloidopathy (by ATXN1 [23,24]) and immune responses (by CD33 [23,25]), further supporting the ‘amyloid hypothesis’ of AD.

**Visual deficits in AD patients**

Considerable evidence shows that AD usually presents with visual deficits in the eye, in addition to the primary complaint of cognitive decline [1]. For example, one piece of evidence is that visual disturbance is often an early complaint of AD patients, which may occur earlier than cognitive impairment [5]. Particularly, the visual impairment include deficiency in color vision and blindness [6,7], visual field loss [26], and backward masking reduction [27]. The second piece of evidence is that there is a significantly higher prevalence of visual deficits in AD patients compared to the normal population [27]. Third, visual analyses show heterogeneity in visual deficiency in AD patients: they tend to have high vulnerability in pattern vision, moderate vulnerability in spatial vision, and low vulnerability in motion and flicker perception [27]. Additionally, numerous studies also reported various anatomical changes in AD eye, including the changes in the pupil (enhanced pupil response to cholinergic drops [26,28]), the lens (supra-nuclear cataract [29]), the retina (thinning in the retinal nerve fiber layer [7]) and the optic disc (pallor, cupping or thinning [6]).

Understanding the physiological functions of the visual system may shed light of the visual deficits commonly seen in AD patients. The eye is a delicate organ of the human body, which processes and communicates outside information to the brain. During visual processing, outside visual information is communicated to the brain through synchronized events. In particular, input light from the outside passes through the cornea, gets focused by the lens, and then reaches the retina. The retina performs essential and complex functions conveying visual message to the brain. The retina contains ten distinct layers of neurons, e.g. the retinal ganglion cell (RGC) layer which generates action potentials, the photoreceptor layer, containing rod and cone cells, which sensitizes retinal ganglion cell (RGC) layer which generates action potentials, the photoreceptor layer, containing rod and cone cells, which sensitizes the retina to light, and the optic disc (pallor, cupping or thinning [6]).

The underlying mechanism of visual deficits in AD has not been fully identified. The mechanism may be related to the same embryonic origin (neuro-ectoderm) for both the eye and the brain [32,33]; thus they may suffer from common pathogenic triggers from genetic and environmental circumstances. The mechanism may also be associated with inflammatory reactions in both the eye and the brain. Increasing evidence shows that AD is characterized by a systemic inflammation [34-36], which accompanies the course of cognitive decline. These inflammatory reactions include increases in both acute and chronic systemic inflammatory activities, and increases in the levels of serum tumor necrosis factor alpha [34-36]. Additionally recent unbiased genome-wide association studies identified variance in genes, e.g. CD33 [23,25], which encode proteins involved in the immune system, suggesting that the immune response plays pivotal roles in AD. Thus the systemic immune responses may account for the functional deficits in both the eye and the brain, which share the same embryonic origin.

**Amyloidopathy in human eye disorders**

Besides the general complaints of visual deficits, AD patients have a significantly increased chance to develop specific eye disorders, e.g. open-angle glaucoma (OAG) [37,38]. Emerging evidence shows the involvement of amyloidopathy in several eye disorders related to AD. For example, Aβ levels/plaques are significantly higher in the lens [29] and the retina [39] in AD group compared to control group. Amyloidopathy has also been identified in common visual disorders, e.g. age-related macular degeneration (AMD) and cataract. The several following paragraphs will review the involvement of amyloidopathy in these eye disorders.

**Open-angle glaucoma (OAG)**

Glaucoma is a chronic and degenerative neuropathy, often characterized by the loss of RGC and the presentation of optic nerve cupping. Primary OAG is classified by the appearance of the iridocorneal angle. It affects a large percentage of the population, and is in fact the second leading cause of blindness in the U.S. alone and the leading cause of blindness among African Americans in the world [40]. Evidence from independent research groups suggests that AD patients have an increased rate of occurrence with glaucoma, particularly OAG [37]. Bayer et al. showed that the prevalence of probable glaucoma in AD patients (24.5%) was significantly higher than that of the control group (6.5%) [37]. Interestingly, all patients with glaucoma in the study had primary OAG. Subsequently, Tamura and colleagues obtained similar results in Japanese population [38]. They investigated whether the prevalence of OAG in AD patients differed from an age-matched control group in the Japanese population. Their studies showed that the prevalence of OAG (23.8%) in AD patients was significantly higher than that of the control population (9.9%) [38]. Collectively, these results suggest that common pathogenic factors may contribute to both AD and OAG [38].

**Age-related macular degeneration (AMD)**

Age-related macular degeneration [AMD] is the leading cause of central blindness in people who are over 50 years old in the world [41]. AMD is pathologically characterized by the presence of drusen, which are extracellular deposits that accumulate beneath the retinal pigmented epithelium. Recent studies showed that drusen also contained substantial Aβ species which displayed different conformations based on antibody reactivity, in addition to apolipoprotein E and various complement components, e.g. C5, C5b9 complex, and C3 fragments [42]. Antibodies, including 6E10 which recognizes the first 16 amino acids of AD Aβ (anti-Aβ [1-16]; DAEFRHDSGYEVHHQK) [43], showed strong immune-activity in both AD brain senile plaques [anticipated; positive control] and drusen in the eye. The electron microscopy was utilized as an independent approach to identify amyloid fibrils in drusen [42]. Collectively, drusen contains the same Aβ species as those in AD brain, suggesting that Aβ accumulation is a key pathogenic determinant linking the pathology in both AMD and AD [42].

**Cataract**

Besides AMD and OAG, the cataract is another common eye disorder with aging as the primary risk factor. It is common in people over the age of 60 and is the leading cause of blindness worldwide [44]. The cataract is caused by a clouding in the lens often due to protein aggregation [44]. The clouding impairs the focusing of input light as
Amyloidopathy in AD mouse models

Model organisms provide a powerful tool for identifying and characterizing the mechanisms of AD and potential treatment/cure of human disorders, including AD. For example, different animal models have been developed to investigate AD, including zebrafish [46-48], Caenorhabditis elegans [49-51], Drosophila [52,53], and mouse [54-58]. Considerable evidence from these AD animal models shows amyloidopathy and cognitive decline, as well as visual deficits, recapitulating the pathology in AD patients. Next, this article will describe several widely-utilized AD mouse models, focusing on the results in the eye, with an aim to emphasize the significant roles of amyloidopathy in visual deficits.

Tg2576 is one of the earliest and well-characterized AD transgenic mouse models [54-58]. It carries the APP Swedish mutation (Lys670Asn/Met671Leu) and features increased Aβ levels in the brain, as well as age-related behavioral impairment, and synaptic deficits [54-58]. Several groups have shown amyloidopathy in the eye of Tg2576 mice [59,60]. In one study, Dutescu and colleagues using 14 month old Tg2576 mice found strong APP expression in the inner nuclear layer and ganglion cell layer of the retina, as well as in the lens and the cornea [59]. They also found weak APP expression in the photoreceptor and retinal pigmented epithelial cell layer. In addition, Western blot analysis using Tg2576 and control mouse samples showed the expression of full-length APP and several APP cleavage products range 18-70 kDa in molecular weight from the retina and the brain. The authors studied retina and brain Aβ levels and found that both Aβ40 and Aβ42 levels from the retina were lower than those in the brain of Tg2576 mice. Finally, they found that levels of both Aβ40 and Aβ42 in the retina of Tg2576 mice were much higher than in the control mice [60]. Ning et al. compared the temporal and spatial expression patterns of APP, Aβ deposits and inflammatory reactions in the retina of these mice [64]. They found age-dependent increases in APP expression and Aβ deposition in multiple layers of the retina. In addition, Aβ accumulation was accompanied by increased immuno-reactivity and apoptotic processes in the RGC [64].

Concluding remarks and future perspectives

Despite a relative lack of knowledge of the tauopathy and the APP proteolytic secretases in the eye compared to the well-characterized amyloidopathy, there has been clearly an enormous progress in understanding the visual impairment associated with AD. AD is the primary cause of dementia with complex underlying mechanisms and it often presents with concomitant visual impairment. Multidisciplinary studies from genetics, biochemistry, cell and molecular biology using cell-based models, animal-based models, as well as human specimens provide evidence that the pathogenesis of AD is primarily caused by Aβ accumulation and deposition in the brain. Here we reviewed the visual deficits of AD and the involvement of amyloidopathy in several common human visual disorders, and then we discussed the amyloidopathy in the eyes of several AD mouse models. Collectively, these studies discussed in this article suggest the significant role of Aβ in the pathogenesis of visual deficits and eye disorders. These studies also further support the “amyloid hypothesis” of AD.

Emerging evidence supports the idea that the eye may provide a “window” in the screening, early diagnosis or monitoring the treatment of AD. Currently a definite diagnosis of AD can only be confirmed post-mortem, and a pre-mortem diagnosis of AD is primarily dependent on the evaluations of cognitive and memory impairment [65,66]. Due to the shared amyloidopathy of the eye and the brain in AD, developing non-invasive ocular analyses may advance the AD clinical practice. For example, based on the aggregation in the lens caused by the amyloid or other proteins [29,44], the quasi-elastic laser light scattering spectroscopy has been utilized to detect and monitor these aggregates in mouse models [67]. In addition, a novel high-resolution retinal plaque-imaging technique was developed to label Aβ plaques in live AD mice and post-mortem retinal samples of AD patients [39]. Thus, developing and utilizing non-invasive ocular tests, (e.g. the quasi-elastic laser light scattering spectroscopy, or probe-based retinal imaging) may support the earlier screening of AD patients, monitoring of the disease progress and assessing the therapeutic efficacy of AD.

References

1. Cummings JL (2004) Alzheimer's disease. N Engl J Med 351: 56-67.

2. Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics, Science 297: 353-356.
3. Bertram L, Tanzi RE (2008) Thirty years of Alzheimer's disease genetics: the implications of systematic meta-analyses. Nat Rev Neurosci 9: 768-778.
4. Gandy S (2005) The role of cerebral amyloid beta accumulation in common forms of Alzheimer disease. J Clin Invest 115: 1121-1129.
5. Sadun AA, Borchert M, Deviia E, Hinton DR, Bassi CJ (1987) Assessment of visual impairment in patients with Alzheimer’s disease. Am J Ophthalmol 104: 113-120.
6. Cronin-Golomb A, Sugira R, Corkin S, Growdon JH (1993) Incomplete achromatopsia in Alzheimer's disease. Neurobiol Aging 14: 471-477.
7. Pachc M, Smeets CH, Gioso PF, Savaskan E, Flammer J, et al. (2003) Colour vision deficiencies in Alzheimer's disease. Age Ageing 32: 422-426.
8. Tanzi RE, Bertram L (2005) Twenty years of the Alzheimer's disease amyloid hypothesis: a genetic perspective. Cell 120: 545-555.
9. Selko DJ, American College of Physicians, American Physiological Society (2004) Alzheimer disease: mechanistic understanding predicts novel therapies. Ann Intern Med 140: 627-638.
10. Wright AF (2005) Neurogenetics II: complex disorders. J Neurol Neurosurg Psychiatry 76: 623-631.
11. Selko DJ (2001) Alzheimer's disease: genes, proteins, and therapy. Physiol Rev 81: 741-766.
12. Tanzi RE, Bertram L (2001) New frontiers in Alzheimer's disease genetics. Neuroon 32: 181-184.
13. Vassar R, Bennett BD, Babu-Khan S, Kahn S, Mendiza EA, et al. (1999) Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. Science 286: 735-741.
14. Kimberly WT, Lavie MJ, Ostaszewski BL, Ye W, Wolfe MS, et al. (2003) Gamma-secretase is a membrane protein complex comprised of presenilin, nicasrin, Aπh-1, and Pen-2. Proc Natl Acad Sci U S A 100: 6382-6387.
15. Sisodia SS, St George-Hyslop PH (2002) gamma-Secretase, Notch, Abeta and Alzheimer's disease: where do the presenilins fit in? Nat Rev Neurosci 3: 281-290.
16. Zhang C, Saunders AJ (2007) Therapeutic targeting of the alpha-secretase pathway to treat Alzheimer's disease. Discov Med 7: 113-117.
17. Nikolaev A, McLaughlin T, O'leary DD, Tessier-Lavigne M (2009) APP binds DR6 to trigger axon pruning and neuron death via distinct caspases. Nature 457: 981-989.
18. Zhang C, Browne A, Kim DY, Tanzi RE (2010) Familial Alzheimer's disease mutations in presenilin 1 do not alter levels of the secreted amyloid-beta protein precursor generated by beta-secretase cleavage. Curr Alzheimer Res 7: 21-26.
19. Tanzi RE, Gusella JF, Watkins PC, Bruns GA, St George-Hyslop P, et al. (1987) Amyloid beta protein gene: cDNA, mRNA distribution, and genetic linkage near the Alzheimer locus. Science 235: 880-884.
20. Strittmatter WJ, Saunders AM, Schmechel DE, Pericak-Vance MA, Englund J, et al. (1993) Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci U S A 90: 1977-1981.
21. Gatz M, Reynolds CA, Fratiglioni L, Mortimer JA, et al. (2006) Role of genes and environments for explaining Alzheimer disease. Arch Gen Psychiatry 63: 186-174.
22. Bertram L, Lill CM, Tanzi RE (2010) The genetics of Alzheimer disease: back to the future. Neuro 68: 270-281.
23. Bertram L, Lange C, Mullin K, Parkinson M, Hsiao M, et al. (2008) Genome-wide Association Analysis Reveals Putative Alzheimer's Disease Susceptibility Loci in Addition to APOE. Am J Hum Genet 83: 623-632.
24. Zhang C, Browne A, Child D, Divito JR, Stevenson JA, et al. (2010) Loss of function of ATXN1 increases amyloid beta-protein levels by potentiating beta-secretase processing of beta-amyloid precursor protein. J Biol Chem 285: 8515-8526.
25. Naj AC, Jun G, Beecham GW, Wang LS, Vardarajan BN, et al. (2011) Common variants at MS4A4A/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. Nat Genet 43: 436-441.
26. Trick GL, Trick LR, Morris P, Wolf M (1995) Visual field loss in senile dementia of the Alzheimer's type. Neurology 45: 68-74.
of a transgenic Caenorhabditis elegans expressing neuronal amyloid-beta. J Alzheimers Dis 19: 681-690.

51. Dostal V, Link CD (2010) Assaying beta-amyloid toxicity using a transgenic C. elegans model. J Vis Exp pii: 2252.

52. Li A, Xie Z, Dong Y, Mckay KM, Mckee ML, et al. (2007) Isolation and characterization of the Drosophila ubiquitin ortholog dUbq01 in vivo interaction with early-onset Alzheimer disease genes. Hum Mol Genet 16: 2626-2639.

53. Ganguly A, Feldman RM, Guo M (2008) ubiquitin antagonizes presenilin and promotes neurodegeneration in Drosophila. Hum Mol Genet 17: 293-302.

54. Hsiao K, Chapman P, Nilsen S, Eckman C, Harigaya Y, et al. (1996) Correlative memory deficits, Abeta elevation, and amyloid plaques in transgenic mice. Science 274: 99-102.

55. Jacobsen JS, Wu CC, Redwine JM, Comery TA, Arias R, et al. (2006) Early-onset behavioral and synaptic deficits in a mouse model of Alzheimer's disease. Proc Natl Acad Sci U S A 103: 5161-5166.

56. Kawarabayashi T, Younkin LH, Saido TC, Shoji M, Ashe KH, et al. (2001) Age-dependent changes in brain, CSF, and plasma amyloid (beta) protein in the Tg2576 transgenic mouse model of Alzheimer's disease. J Neurosci 21: 372-81.

57. Chapman PF, White GL, Jones MW, Cooper-Blacketer D, Marshall VJ, et al. (1999) Impaired synaptic plasticity and learning in aged amyloid precursor protein transgenic mice, Nat Neurosci 2: 271-276.

58. Massaad CA, Washington TM, Pautler RG, Klann E (2009) Overexpression of SOD-2 reduces hippocampal superoxide and prevents memory deficits in a mouse model of Alzheimer's disease. Proc Natl Acad Sci U S A 106: 13576-13581.

59. Dutescu RM, Li QX, Crowston J, Masters CL, Baird PN, et al. (2009) Amyloid precursor protein processing and retinal pathology in mouse models of Alzheimer's disease. Graefes Arch Clin Exp Ophthalmol 247: 1213-1221.

60. Liu B, Rasool S, Yang Z, Glabe CG, Schreiber SS, et al. (2009) Amyloid- peptide vaccinations reduce (beta)-amyloid plaques but exacerbate vascular deposition and inflammation in the retina of Alzheimer's transgenic mice. Am J Pathol 175: 2099-2110.

61. Savonenko A, Xu GM, Melnikova T, Morton JL, Gonzalez V, et al. (2005) Episodic-like memory deficits in the APPswe/PS1dE9 mouse model of Alzheimer's disease: relationships to beta-amyloid deposition and neurotransmitter abnormalities. Neurobiol Dis 18: 602-617.

62. Jankowsky JL, Fadale DJ, Anderson J, Xu GM, Gonzales V, et al. (2004) Mutant presenilins specifically elevate the levels of the 42 residue beta-amyloid peptide in vivo: evidence for augmentation of a 42-specific gamma secretase. Hum Mol Genet 13: 159-170.

63. Borchelt DR, Ratovitski T, Van Lare J, Lee MK, Gonzales V, et al. (1997) Accelerated amyloid deposition in the brains of transgenic mice coexpressing mutant presenilin 1 and amyloid precursor proteins. Neuron 19: 939-945.

64. Ning A, Cui J, To E, Ashe KH, Matsuura J (2008) Amyloid-beta deposits lead to retinal degeneration in a mouse model of Alzheimer disease. Invest Ophthalmol Vis Sci 49: 5136-5143.

65. Thal LJ, Kantarci K, Reiman EM, Klunk WE, Weiner MW, et al. (2006) The role of biomarkers in clinical trials for Alzheimer disease. Alzheimer Dis Assoc Disord 20: 6-15.

66. Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns N, et al. (2012) National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement 8: 1-13.

67. Muchowski PJ, Ramsden R, Nguyen Q, Arnett EE, Greiling TM, et al. (2008) Noninvasive measurement of protein aggregation by mutant huntingtin fragments or alpha-synuclein in the lens. J Biol Chem 283: 6330-6336.