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# Ophthalmology Perspective on The Theory of Amyloid Beta Toxicity: Implications on Future Studies

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### Background

The debate about the theory of amyloid beta (A $\beta$ ) toxicity grew after the recent approval of the Alzheimer's drug Aducanumab. This was especially true after one of the first articles to bring up this theory was recently criticized for being questionable. Several studies in the field of ophthalmology also used the same theory of A $\beta$  toxicity. We examined the breadth of A $\beta$ -related ophthalmology articles, with an emphasis on those that address A $\beta$  toxicity theory.

### Methods

We searched PubMed for ophthalmology-related articles until January 2024, mentioning amyloid beta to study the consequences of such data concerns and questioned the pathogenic role for A $\beta$ .

### Results

There was a total of 451 articles in the field of ophthalmology that talked about A $\beta$ . Before 2007, the number of articles did not exceed 10 per year. Since 2007, the number of articles published each year has gone up. In 2007, 14 articles were published, by 2021, 38 articles were published each year before decreasing to 24 articles by 2023. The 2006 article by Lesne et al. was cited 1216 times in PubMed. When both searches were put together, a total of seven ophthalmology-related articles that cited Lesne et al's article were found, which we discussed in this review article.

### Conclusion

Most articles on ophthalmology saw amyloid beta as a diagnostic biomarker, but only a few findings demonstrated that it could be toxic. Most of the time, A $\beta$  was talked about in relation to the retina and its age-related disease, age-related macular degeneration.

## INTRODUCTION

The neurology and neuroscience community has been in a debate during the last period on the theory of amyloid beta (A $\beta$ ) pathological role in Alzheimer's disease, a debate that was fueled recently by the expression of concern related to a possible fabrication of a landmark article published in 2006 in *Nature* that suggests a toxic effect of A $\beta$  aggregate.<sup>1</sup> The discussion about the toxic effect of A $\beta$  peaked after the United States Food and Drug Administration (USFDA) ap-

proval of Aducanumab,<sup>2</sup> a monoclonal antibody drug that target A $\beta$  and reduce their size, however, with limited clinical impact.<sup>3</sup> While Lesne et al's study directly investigated the pathological role of A $\beta$  on animal's brain,<sup>1</sup> there have been other studies investigating the pathological role of A $\beta$  from other perspectives and supported the A $\beta$  hypothesis in Alzheimer's disease.

Among the major advances in this regard are studies on  $\gamma$ -secretase, an enzyme that cleaves its immediate substrat and was shown to be a potential target for therapies.<sup>4</sup> Other

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older evidence emerged from studies on Alzheimer's disease patients and patients with Down syndrome, showed similarities in A $\beta$  deposition in meningeal vessels.<sup>5</sup> This is also in concordance with emerging studies from longitudinal follow-up of patients with autosomal dominant Alzheimer's disease, where higher A $\beta$  levels are associated with poor clinical outcome.<sup>6</sup>

In ophthalmology, a field that is closely related to neurology, there has been extensive research on A $\beta$  role in the eyes, where research into A $\beta$  has been mostly directed toward its diagnostic value for neurological and ophthalmic diseases,<sup>7</sup> few studies suggested a pathological role for the A $\beta$ , and such studies stemmed mostly from what was known about its role in Alzheimer's disease.<sup>8</sup> Here, we will assess the ophthalmic research that discussed A $\beta$ , where we will focus on articles citing Lesne et al's 2006 article that suggested a pathological role for A $\beta$  and had recently an expression of concern.<sup>1</sup>

## METHODS

To investigate the implications of such data concern and questioned pathological role for A $\beta$ , we performed a PubMed search on for articles in ophthalmology discussing amyloid beta till the 1<sup>st</sup> of January 2024. We first performed a search on Medical Subject Heading database (MeSH database) to extract relevant keywords. We then used advanced search on PubMed using the following search strategy: (Amyloid beta-Peptides[MeSH Terms] OR A $\beta$ [Title/Abstract] OR "Amyloid beta"[Title/Abstract] OR "Alzheimer beta-Protein"[Title/Abstract] ) AND (eye[MeSH Major Topic] OR "macular degeneration"[Title/Abstract] OR "glaucoma"[Title/Abstract] OR "cataract"[Title/Abstract] OR "Pseudoexfoliation syndrome"[Title/Abstract] OR "retinopathy"[Title/Abstract]).

This was followed by a search in Lesne et al's 2006 article's citations on PubMed. Finally, combining both previous searches using "AND" operator yielded ophthalmology articles discussing pathological role of A $\beta$  directly impacted by Lesne et al's 2006 article.

We used VOSviewer version 1.6.16 for literature mapping, where it can be used to analyze the keywords, most appeared in studies, which represents major topics discussed.<sup>9</sup> We specified an occurrence threshold of 10 times to be further included in the analysis and mapping. VOSviewer calculate an indication of how strong an item connected to others; an indicator called "Total link strength".<sup>9</sup>

## RESULTS

There was a total of 452 ophthalmology articles discussing A $\beta$ . The yearly number of articles did not exceed 10 articles till 2007. Since 2007, the yearly number of published articles has increased from 14 articles per year in 2007, reaching 38 articles per year in 2021 however decreased back to 25 articles per year in 2023. In PubMed, Lesne et al's 2006 article received a total of 1216 citations. In total, seven articles related to ophthalmology that cited Lesne et al's article has

been found when combining both previous searches, and they will be discussed further below.

Supplementary figure 1 shows the most common keywords used in the searched articles that occurred above the prespecified threshold. These keywords had the strongest linkage with A $\beta$  and included "age-related macular degeneration" (link strength 4) and "glaucoma" (link strength 1) as the most common diseases, "oxidative stress" (link strength 1) as the most common process, and "retina" (link strength 3) and its "retinal pigment epithelium" (link strength 2) as the most commonly appearing structures.

## DISCUSSION

While the diagnostic role for A $\beta$  for aging and its related diseases has been the subject of research for decades, being a target for therapy has been criticized intensively, even after the approval of the first Alzheimer's drug that works directly on amyloid beta. For the ophthalmic community and until further evidence arises. Studies generally considered A $\beta$  as a biomarker for the diagnosis of Alzheimer's disease. Invasive methods such as cerebrospinal fluid (CSF) analysis are used internationally in aid of detecting A $\beta$  in AD.<sup>10</sup> Despite the CSF analysis otherwise fascinating accuracy in detecting and predicting the outcome of the disease,<sup>11,12</sup> it is not only the invasiveness of the analysis that makes the diagnosis process harder but also the high financial cost and time needed to get the results.<sup>13</sup> However recent efforts have been directed towards finding less invasive methods such as plasma A $\beta$  detection a theory that has been extensively reviewed.<sup>14</sup> Several potential blood biomarkers have been studied such as proteins, lipids, oxidative-stress-related molecules, and cytokines.<sup>15</sup> However, amyloid- $\beta$  (A $\beta$ ) levels show the highest potential in this matter.<sup>16</sup> Interestingly, amyloid- $\beta$  (A $\beta$ ) is linked with neurodegenerative ocular diseases such as age-related macular degeneration (AMD) by being the major constituent of the retina drusen of the eye.<sup>17</sup> This subsequently strengthens the relationship between amyloid- $\beta$  (A $\beta$ ) in AD and different ophthalmic disorders. As a diagnostic connection between ophthalmology and AD, A $\beta$  levels in tear fluids were also considered a possible biomarker for AD after finding a significant increase in AD patients compared to controls.<sup>18</sup> A study by Masuzzo et al., suggests that the retina maybe the "window to brain" as early pathology in eyes could predict AD.<sup>19</sup> Eyes actually contain many potential biomarkers such as nerve and vascular damage which could be detected via ophthalmic imaging techniques, offering valuable insights into the early diagnosis of neurodegenerative diseases, with detection of A $\beta$ -related retinal changes being the most promising marker.<sup>20</sup> Detecting ocular biomarkers via retinal imaging provides a cost-effective approach in large-scale AD diagnosis and monitoring.<sup>21,22</sup> Various ocular imaging techniques, including Optical coherence tomography (OCT) and scanning laser ophthalmoscopy (SLO) are available, each used to detect specific biomarkers.<sup>20</sup> OCT of the retina is a fast and feasible tool used to diagnose AD by the quantification of optic nerve topography and nerve fiber layer, however not yet specific to the disease.<sup>23</sup>

In a study on patients with subjective cognitive decline, using OCT imaging, macular thickening specifically at the inner nasal region was significantly associated with A $\beta$  deposition in the retina.<sup>24</sup> Like OCT, SLO is used to visualize structures of the retina however, using laser beams instead of interferometry used in OCT.<sup>25</sup> In Alzheimer's disease Adaptive optics scanning laser ophthalmoscopy (AOSLO) a type of SLO was used by Zhang et al to propose the presence of granular membranes surrounding the optic nerve as a new potential biomarker of early AD.<sup>26</sup> Radio and neurological imaging such as brain positron emission tomography (PET) scan and magnetic resonance imaging (MRI) have also been implemented in the aid of early diagnosis of A $\beta$  related pathologies.<sup>27</sup> In PET scan of the brain, radioactive compounds most lately being Florbetaben, Florbetapir and Flutemetamol are injected to the patient. These compounds selectively stain A $\beta$  in the brain due to their chemical characteristics and lipophilicity.<sup>28</sup> PET scan has the advantage of being a time efficient technique which accurately detects A $\beta$  aggregates in the brain making it a reliable diagnostic technique. Still, positive PET scan results are not specific to AD since any other A $\beta$  pathology would yield a positive result.<sup>29</sup> Magnetic Resonance Imaging (MRI) has played a role in diagnosing Alzheimer's disease for several decades and still does now.<sup>30</sup> The clinical role of MRI has mostly been the detection of brain atrophy especially the medial temporal lobe (MTL) which includes the entorhinal cortex (ERC) and hippocampus which could discriminate AD from other neurodegenerative illnesses.<sup>31</sup> Recently Sulheim et al reported promising results of using luminescent conjugated oligothiophenes (LCOs) to target A $\beta$  deposits and detect them via MRI which could be safer than PET scan since MRI doesn't require radioactive molecules.<sup>32</sup> The critical role of developing less invasive and faster diagnostic methods stems from the fact that, the earlier in course we detect neuro-degenerative diseases the easier and better is the clinical management required,<sup>33</sup> that is why the search of such techniques is finding an increased attention. In the era of advanced technology, artificial intelligence started to be enrolled in medical diagnosis whether via interpreting diagnostic images or detecting biomarkers.<sup>34</sup> AI has been used in AD for various purposes ranging from early detection to even the evaluation of therapy and in a similar way similarly to diagnose AMD.<sup>35,36</sup> On the other hand, the pathologic and toxic effect of amyloid beta was debatable, especially since studies showed that even high level of amyloid beta in patients with amyloidosis had no toxic effects.<sup>37</sup>

In the seven ophthalmic studies that cited Lesne et al's article, as shown in supplementary table 1 four of them suggested a toxic effect of A $\beta$ .<sup>19,38-40</sup> Three of the four studies agreed on the impact of amyloid- $\beta$  (A $\beta$ ) on microglial activation as a form of toxic effect.<sup>19,38,39</sup> Only one article suggested a "little doubt" about the toxic effect of A $\beta$  aggregates,<sup>41</sup> and one article suggested a role for A $\beta$  in the neurodevelopment of the retina.<sup>42</sup> The potential of using the presence of amyloid- $\beta$  (A $\beta$ ) pathology in lenses as a biomarker for early detection and continual monitoring of AD was suggested by the most recent paper citing

Lesne et al's article.<sup>43</sup> Supplementary table 1 further discusses all seven articles summarizing their study design, major findings and most importantly the role of A $\beta$  in each study and implications for the sector of ophthalmology.

Microglial activation has been reported to be a major contributor to the neurotoxicity seen in AD, with amyloid- $\beta$  (A $\beta$ ) acting as a critical contributor to this activation. Overactive microglial cells lose the ability to eliminate A $\beta$  via phagocytosis, which was reported to be involved in the cognitive decline seen in AD.<sup>44</sup> Similarly, microglial activation was mentioned to have a pathological role in different age-related eye diseases such as AMD.<sup>45</sup> The pivotal role of microglia directed the search to certain targets in the microglial activation cascade as possible biomarkers for AD and other degenerative eye disorders.<sup>46</sup>

$\gamma$ -Secretase is a transmembrane protein complex that mediates the final cleavage of APP which eventually liberates A $\beta$ .<sup>47</sup>  $\gamma$ -Secretase inhibitors were shown to be a potential approach for treating Alzheimer's,<sup>4</sup> but there are worries about their deleterious side effects, namely, worsening of the cognitive, functional, and clinical performances.<sup>48</sup> In ophthalmology, a recent study on rats concluded that  $\gamma$ -Secretase inhibitors might provide a therapeutic approach in prevention and treatment of subretinal fibrosis in neovascular AMD and other fibrovascular diseases.<sup>49</sup>

Apolipoprotein E (APOE) is a major lipoprotein in the brain, and the APOE4 isoform expression remains the greatest genetic risk factor for Alzheimer's, which causes an increase in A $\beta$  deposition and pathology.<sup>50</sup> In ophthalmology, APOE4 isoform expression has been suggested to be a protective factor in primary open angle glaucoma, a form of chronic neuropathy,<sup>51</sup> despite the inconsistencies in literature.<sup>52</sup> Most recently, an animal study showed that mice with targeted deletion of APOE in microglia were protected from retinal ganglion cell (RGC) loss.<sup>53</sup> These results in ophthalmology might warrant more studies on the pathological role of A $\beta$  or even its protective role. However, A $\beta$  role as a biomarker is strongly supported by the literature.

## CONCLUSION

While most ophthalmic articles regarded amyloid beta as a diagnostic biomarker, only a few studies suggested a toxic role for it. From all possible toxic effects of Amyloid beta, activation of microglial response and inflammation has been often reported. New diagnostic methods are being tested for different neuro-degenerative diseases in relation to A $\beta$  with promising potential. Retina and its age-related disease, age-related macular degeneration, were the most common topics discussed in conjunction with A $\beta$  with glaucoma being occasionally discussed. A $\beta$  as a therapeutic target is yet to be agreed upon due to the fear of losing its physiological contribution to neurodevelopment. We believe that future studies on A $\beta$  should focus on its diagnostic role until new robust evidence emerges.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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## SUPPLEMENTARY MATERIALS

### **Supplementary material**

Download: [https://hymr.scholasticahq.com/article/94964-ophthalmology-perspective-on-the-theory-of-amyloid-beta-toxicity-implications-on-future-studies/attachment/199626.docx?auth\\_token=S5p4aSlw2qp4iYsM6XDH](https://hymr.scholasticahq.com/article/94964-ophthalmology-perspective-on-the-theory-of-amyloid-beta-toxicity-implications-on-future-studies/attachment/199626.docx?auth_token=S5p4aSlw2qp4iYsM6XDH)

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