Ocular and Visual Manifestation of the Alzheimer's Disease: A Literature Review, Part I: Animal Models and Human Pathology

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Abstract

Context: The retina is a part of the Central Nervous System that is easy to study. The visual disturbances are frequent in Alzheimer's disease (AD) patients and sometimes, the AD begins with visual symptoms. This paper aims to review the existing literature on the involvement of the eye in the AD. In this first part, the animal models and the pathology in humans were examined.

Evidence Acquisition: The Medline literature until March 2018 was surveyed.

Results: Both animal models and pathological studies in humans demonstrate the impairment of the visual system in the AD, often in the early stages.

Conclusions: A frequent and sometimes early involvement of the visual system was demonstrated but new studies are needed in order to investigate the degree of the visual impairment and in the animal models, the importance of the visual deficits in evaluating the cognitive deficits.

Keywords: Alzheimer's Disease, Model of Alzheimer, Vision and Alzheimer, Pathology in Alzheimer, Visual Pathways in Alzheimer

1. Context

The Alzheimer's Disease (AD) is normally regarded as a cognitive disease. However, evidence shows the typical lesions of the AD not only in the brain but also in the spinal cord or even outside the Central Nervous System (CNS). Non-cognitive symptoms, mostly motor or psychiatric symptoms, are also recurrent in the AD (1). The retina is a part of the CNS easy to study. The visual disturbances are frequent in AD patients (2) and sometimes the AD begins with visual symptoms (3). Therefore, many researchers examined the eye and particularly the retina to confirm the diagnosis and monitor the disease's development and its response to drugs. This paper aims to review the existing literature on the involvement of the eye in the AD. In this first part, the animal models and the pathology in humans were examined.

2. Evidence Acquisition

The Medline literature until March 2018 was surveyed using "model of AD", "transgenic model of AD", "ocular changes in model of AD", "vision in AD", and "visual impairment in AD" as keywords. Others studies were identified by reviewing the relevant bibliography quoted in the original papers.

3. Results

3.1. Animal Models

Ning et al. (4) showed amyloid ß (Aβ) deposits in the ganglion cells of the transgenic APP/PS1 mouse and in the neurons of the inner nuclear layer of the retina which both accumulate with age. Perez et al. (5) found retinal Aβ plaques in the APPswe/PS1ΔE9 transgenic mouse at the age of 12 - 13 months associated with a significant increase in microglial activity. In the brain of these mice, Aβ plaques were found at the age of 2 - 6 months. Accordingly, the authors reported electroretinogram abnormalities. In the same model, Gupta et al. (6) confirmed the accumulation of Aβ in the retina, as well as inner retinal degenerative changes. Dutescu et al. (7) found the strong cytoplasmatic expression of the amyloid precursor protein (APP) in the retinal ganglion cells and in inner nuclear layer cells of the lens and corneal epithelia of 2-18-month-old transgenic mice with the double Swedish mutation. In the retinas, the authors also found proteolytic products that had not been detected in the cerebellum. In another rat model, the Tg2576 mouse, Liu et al. (8) found Aβ plaques with

increased retinal microvascular deposition in the retina. Amyloid peptide vaccination reduces retinal Aβ deposits but increases retinal microvascular Aβ deposition and exacerbates microglial infiltration and astrogliosis with disruption of the retinal organization. In the double transgenic mice APPswe/PS1ΔE9, Koronyo-Hamaovi et al. (9) could detect Aβ plaques in vivo, both in the retina and in the brain, after administering curcumin. Because at the age of 2.5 months, plaques could only be detected in the retina but not in the brain, it could be inferred that the retinal damage may be an early AD marker. However, retinal plaques were not detected in another model, the non-Tgwt mice. In this model, Yang et al. (10) confirmed a twofold increase in microglia, prominent inner retinal Aβ, paired helical filament-tau, and decreased retinal ganglion cell layer neurons. They also showed that bone marrow transplantation has a protective action against retinal degeneration, resulted from alterations in the immune function and oxidative stress. Gasparini et al. (11) showed early axonopathy and accumulation of hyperphosphorylated tau in the retinal ganglion cells of P301S transgenic mice at the age of 5 months, both typical indicators of the initial stages of the AD. Blurred optic disc margin was also detected by ophthalmoscopic examination. In the same model, Schon et al. (12) demonstrated in vivo fibrillar tau in the retina and an increase in the tau pathology over several months, thus stressing how the retinal pathology precedes the cerebral pathology; hyperphosphorylated tau was also found in the retinas of 5/6 AD patients. In another AD model, the APP/PS1 mouse, hyper-expression of the phosphorylated tau was equally found in the retina, while there was little or no sign in the optic nerve, in the cornea, and in the lens (13). A marked thinning of the retinal choroid has been observed in the TgF344-AD rat model and in humans; in this model, visual acuity was lower than in age-matched rats (14). Antes et al. (15) studied the effects of Apolipoprotein E4 (APO E4), the most prevalent genetic risk factor for the AD, in transgenic mice. They reported that the synaptic density of the outer and inner retinal plexiform layer was significantly lower in the APO E4 mice than in the APO E3 mice; similarly, the responses to electroretinography were different. The authors hypothesized that both rods and cones pathways are affected by the APO E genotype. Perez de Lara et al. (16) showed an increase in the retinal adenosine triphosphate (ATP) in mice; according to the authors, this may contribute to the changes in the functionality of the retina and in the death of the retinal cells. In the aluminum-fed mice, 5xFAD Tg-AD markers for inflammatory pathology appeared both in the brain and in the retina (17). Edwards et al. (18) focused on macroglia changes in the triple transgenic mouse (3XTG-AD). They found glial activation at 9 months of age that increased with age and abnormal glial structures; besides, the retinal glial activation preceded that in the brain. More and Vince (19) proposed a spectrophotometric technique to detect imaging in early stages of the AD and subsequently detected amyloid aggregates in the retina of transgenic APP/PS1 mouse at 4 months of age, while these were absent in the brain. Oliveira-Souza et al. (20) in the mouse Tg-SwDI noticed cell loss in the photoreceptor layer and inner retina, specific cholinergic cell loss, and increased astrocytic gliosis. Age-related macular degeneration (AMD) is the most common cause of blindness in the aging population. The senescence-accelerated OXYS rats develop cognitive deficit similar to those seen in the AD (21) and Aβ accumulates in the retina causing neurodegeneration and progressive loss of photoreceptors (22). Degeneration of photoreceptors was also observed in a model of Drosophila; interestingly, the degeneration of photoreceptors precedes the appearance of Aβ plaques (23). A promising model is the Octodon Degus, a rodent species endemic to South America, which developed Aβ and tau pathology in the brain and showed a cognitive decline as a result of aging, suggesting that this rodent is a natural model of the AD. Du et al. (24) detected amyloid peptides, oligomers, and phosphorylated tau with a higher incidence in the retina of adult animals. Hurley et al. (25) confirmed these results, as well as the presence of a cataract. Some authors have claimed a reduction in the number of retinal ganglion cells; yet, these results have remained controversial (see Pathology in humans). In particular, Williams et al. (26) conclusions on the reduced dendritic integrity of the retinal ganglion cells accompanied by the absence of soma loss in transgenic animals (Neurobiology of Aging 2013) have been recently disputed. In an accurate work, Chidlow et al. (27) detected amyloid plaques in the cerebral cortex and hippocampus of the APPswe/PS1ΔE9 mouse since the age of four months whereas, in the retina, the plaques were found at the age of 12 months. Moreover, they were unable to demonstrate the presence of dystrophic neurites, retinal thinking, neuronal loss, synaptic shrinkage, gliosis, oxidative stress, tau hyperphosphorylation, upregulation of cytokines, or stress signaling molecules in the retina. Using manganese-enhanced Magnetic Resonance Imaging (MRI). Gallagher et al. (28) demonstrated, in mice knocked for the APP gene, the reduced axonal transport along the fiber tracts from the hippocampus to the amygdala and basal forebrain and in the visual pathways from eye to midbrain and superior colliculus. Two mice models of the AD, one expressing Aβ plaques and another expressing neurofibrillary tangles, were impaired in the visuospatial capabilities and not in the olfactory (29). Finally, in the transgenic mouse, the increased frequency of cataract was found (30).

3.2. Pathology in Humans

In the AD, neurofibrillary tangles and neuritic plaques are usually preeminent in the hippocampus, entorhinal area, and uncus whereas motor, somatic sensory, and primary visual areas are relatively spared (31). In the Lewis' et al. cases (32), neurofibrillary tangles were rarely present in the primary visual cortex, but far more preeminent in the adjacent visual association cortex and even more frequent in the visual association cortex of the inferior temporal gyrus. On the other hand, neuritic plaques showed a less specific distribution. Ikonomovic et al. (33) found reduced choline acetyltransferase activity in the primary visual cortex in the AD patients but not in the MCI. However, in some cases, visual disturbances might be the first symptoms of the so-called visual variant of the AD (34-36). This suggests that selected cortical pathways linking the primary visual regions to the posterior parietal and cingulate visual association cortex may be involved in the early stage of the AD. Hof et al. (37) found an increased number of lesions in the visual areas of the occipital and posterior parietal regions in AD patients presenting with Balint's syndrome. Similarly, using positron emission tomography (PET) in patients with the visual variant of AD, Pietrini et al. (38) and Nestor et al. (39) found selective hypometabolism in the occipitoparietal regions. Hof and Morrison (35) found a selective damage to a subset of pyramidal cells in the primary and secondary visual areas of classical AD patients. Leuba and Saini (40) examined the subcortical visual centres (the lateral geniculate nucleus, the lateral inferior pulvinar, and the superior colliculus) and the primary visual cortex of AD patients without preeminent visual symptoms, finding the evidence of senile plaques and/or neurofibrillary lesions in all the examined regions even more abundant than it had been previously observed. Scinto et al. (41) described a selective damage to the Edinger-Westphal nucleus while the adjacent somatic portion of the oculomotor complex was virtually spared of the pathology. In their opinion, such selective damage may explain the pupillary hypersensitivity often observed in the AD. On the other hand, Rub et al. (42) found lesions also in the early stages of the cortical pathology in the rostral interstitial nucleus of the medial longitudinal fascicle involved in the genesis of vertical saccades. The progression of the cortical pathology and of the interstitial nucleus correlates significantly; nonetheless, in their series, the pathology was significantly less severe in the associated nuclei (the Edinger-Westphal nucleus, the Darkschewitsh nucleus, and the interstitial nucleus of Cajal). According to Rahimi et al. (43), the visual system of patients suffering from tau pathology is progressively affected along the visual pathways at least for a subset of patients. Several authors examined the optic nerve to subsequently reach different conclusions. Hinton et al. (44) and Sadun and Bassi (45) found axonal degeneration of the optic nerve. Similar results were referred by Blanks et al. (46); the same authors also noted that the greatest decrease in neuronal density happened in the foveal region, with the temporal region of the central retina being most severely affected (47). These authors also referred to an extensive loss of neurons mainly in the superior and inferior quadrants and an increased astrocyte/neuron ratio (48). In the optic nerve, Wang et al. (49) found the increased expression of the advanced glycation end products that were involved in the pathogenesis of the AD mediating the transport of the Aβ. These receptors are not specific to the AD but are implicated in other inflammatory or degenerative diseases. Koronio-Hamaovi et al. (9) showed Aβ in the retina; Goldstein et al. (50) and Moncaster et al. (51) found the Aβ in the lenses. La Morgia et al. (52) referred to the age-related loss of optic nerve axons and melanopsin ganglion cell. However, others authors (53-55) did not find any sign of optic nerve degeneration or deposits. Other authors yet indicated only age-related alterations: Loffler et al. (56) found an increase in amyloid precursor protein, Curcio and Drucker (57) a reduced density of retinal ganglion cells, and Leger et al. (58) phospho-independent tau deposits. Extracellular deposits called drusen are present in age-related macular degeneration (AMD); some authors found Aβ peptide (59) or non-fibrillar toxic oligomers (60) in drusens. Yoneda et al. (61) found a decrease in the Aβ and an increase in the tau in the vitreous fluid of patients with diabetic retinopathy or glaucoma. Others claimed a relationship between AMD and Apolipoprotein E (APOE). The APOE-ε2 is associated with an extended risk of AD whereas the APO-ε4 is associated with a lower risk (62). However, these results have been contested (see clinical studies).

4. Discussion

Considering the embryological origin of the retina and the frequency of the visual disturbances in the AD, many authors evaluated the possible involvement of the visual system. Actually, pathological studies showed the typical lesions of the AD in the visual system in the early stages; but not all authors agreed about the stage of the disease when the lesions are detected or about their location and frequency. The relative lack of pathological studies could justify such findings but the existence of great interindividual variability is also possible. The animal models showed the involvement of the visual system; but in this case, not all studies are in agreement possibly because the different models of the AD have different characteristics. For example, in the Tg2576 model, the onset of the AD occurs at the age of 6 months with memory loss (63)

whereas the P301S model shows motor impairment in the early stage ([64](#)). Nevertheless, all models showed retinal alterations even at various extents that sometimes preceded the cerebral lesions and in all models, the alterations are prevalent in the inner layer ([4-7](#), [14](#)). This is of importance considering the role of the visual disturbances in evaluating the learning and the memory ([65](#)). In short, a frequent and sometimes early involvement of the visual system was demonstrated but new studies are needed in order to investigate the degree of the visual impairment and in the animal models, the importance of the visual deficits in evaluating the cognitive deficits.

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