



Ocular and Visual Manifestation of Alzheimer's Disease: A Literature Review II Part: Clinical Studies

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Abstract

Context: Visual disturbances are frequent in Alzheimer's disease (AD) and sometimes AD begins with visual disturbances, therefore many researchers have examined the eyes in order to confirm the diagnosis, to monitor the development of the disease or the response to drugs.

Evidence Acquisition: Medline literature until March 2018.

Results: Several indications suggest an early involvement of the visual system in AD, yet this evidence remains inconclusive. The reason for this uncertainty is two folds: The poor quality of the studies and the fact that some alterations are not unique to the AD, since they also occur in others degenerative CNS diseases.

Conclusions: The eye can be a perfect place for early diagnosis of AD and to evaluate the effectiveness of therapies more studies are needed.

Keywords: Alzheimer's Disease, Central Nervous System, fMRI

1. Context

Usually the Alzheimer's disease (AD) is regarded as a cognitive disease. However, evidence shows typical lesions of AD in the brain as well as in the spinal cord or even outside the central nervous system (CNS). Non-cognitive symptoms, mostly motor or psychiatric, are also recurrent in AD (1). The retina is part of the CNS and is easy to study. On the other hand, visual disturbances are frequent in AD patients (2) and sometimes AD begins with visual symptoms (3). Therefore, many researchers have examined the eyes and mainly the retina in order to confirm the diagnosis, to monitor the development of the disease or the response to drugs. The aim of this work was to review the literature in regards to the involvement of the eye in AD. In the first part, this research examined the involvement of the visual system in animal models and in pathological studies in humans; in the second part, clinical studies were reviewed.

2. Evidence Acquisition

Medline literature until March 2018 was scanned using "ocular disease and AD" and "ocular biomarker and AD", as keywords. When ocular disturbances were identified,

the search was narrowed using "ocular saccades and AD", "optic nerve and AD", "retina and AD", "glaucoma and AD", "cataract and AD", and "age-related maculopathy and AD". Additional studies were identified by reviewing relevant bibliography quoted in the original papers. Clinical studies were included in this review whenever they could meet three fundamental criteria: (1) AD diagnosis according to NINCDS-ADRDA criteria (4); (2) studies including patients with dementias other than AD were considered when sufficient data on AD was provided; (3) use of standardized instruments of evaluation.

3. Results

Alzheimer's disease normally has an amnesic presentation, yet a non-amnesic presentation is also possible and in fact some claim that the memory function and the visuomotor function are equally impaired (5). The visual variant of the AD was described by Grunthal (6); in Snowden's et al. series (7) the frequency was 5%. The authors did not notice any discrepancy with classical AD concerning gender distribution, age at onset, neurological signs, family history of dementia, and APOE. While the opening symptoms may be non-specific and the ophthalmic examination normal, some specific deficits might characterize

certain cases. In their series, Lee and Martin (8) referred homonymous visual field loss in four out of eight patients and cortical visual impairment in two out of eight. In rare cases, the authors detected a complete Balint's syndrome (simultanagnosia, oculomotor apraxia and optic ataxia) (6). The MRI showed atrophy in the parieto-occipital regions and the single-photon emission computed tomography (SPECT) and PET decreased metabolism or hypoperfusion in the same regions (3, 9). However, in the classical form, AD disturbances of the visual pathway were documented. The analysis of visual signals is processed through two pathways: the ventral pathway, the so-called "what pathway", begins in the V1 area of the occipital cortex and reaches the temporal lobe. This pathway is involved in the perception and identification of objects and in long-term memory. The dorsal pathway, the so-called "where pathway", begins in the V1 area of the occipital cortex and reaches the parietal lobe and is associated with visuospatial processing, spatial working memory, and visually-guided actions (10). Mentis et al. (11) showed decreased regional cerebral flow in the striate; the authors hypothesized a greater magnocellular dysfunction. Using functional MRI (fMRI) in MCI patients, Teipel et al. (12) found a positive correlation between the activation of the fusiform gyrus and the ventral temporal lobes and a negative correlation with the frontal lobes. By using fMRI, Vannini et al. (13) showed alterations of the visual pathway, suggesting a failure to modulate the neural response to increased task demand. Thulborn et al. (14) showed lesser parietal activation and greater prefrontal activation. These results were confirmed by Prvulovic et al. (15), along with greater activity of the fusiform gyrus; the authors hypothesize a mechanism to compensate for the reduced functional capacity of the superior parietal lobule. Using fMRI in MCI patients, Bokde et al. (16) showed no selective activation of the visual system's pathway; instead, they found higher activation in the frontal lobes. On the other side, Alichniewicz et al. (17) found decreased activation in frontal eyes fields, and Jacobs et al. (18) found increased activation in the visual pathways of MCI and early AD patients. By using diffusion tensor imaging, Nishioka et al. (19) demonstrated that the visual pathway from the eyes to the brain is affected both in the MCI and, to a greater extent, in the AD; pathological changes were found mainly in the optic nerves. In a heterogeneous series of patients with tau pathology, Rahimi et al. (20) found tau deposition both in the optic nerve and in the lateral geniculate nucleus. The visual pathways were also examined using visual evoked potentials (VEP) with conflicting results. By using pattern VEP, some Authors described prolonged latencies (21), whereas others found prolonged latencies only by flash VEP (22). Studies based on flash VEP also found differences between patients

and control groups; however, for a single patient the difference was too small to contribute to the diagnosis (23). Reduced amplitude also positively correlated with the degree of the cognitive impairment (24). Relying on electroretinogram (ERG) and VEP, Sartucci et al. (25) suggest a primary disfunction of the magnocellular stream. Ponomareva et al. (26) found prolonged latencies among the relatives of the patients and Rosengarten et al. (27) claimed that patients with APOE4 have latencies significantly longer than patients without APOE4. Finally, Leinonen et al. (28) found normal VEP in the A β PP/PS1 mice while the ERG shortened in latency, thus, suggesting changes only in the retina.

Several authors examined visual deficits using neuropsychological tests and reaching discordant results. Indeed some recognized visuospatial deficits in the early stages (5, 29) whereas others found evidence only in the latter stages of the disease (30, 31). According to Paxton et al. (30), these deficits may be useful in tracking the disease's course. Some authors identified a selective damage of the posterior pathway (32) whereas others claimed that AD affects multiple visual pathways and regions (29). The ocular motility is controlled by a complex network (33), which can easily be damaged by pathological processes and has therefore been extensively examined in AD research. Several authors reported increased latency to initiate saccades (34-36), while Shakespeare et al. (37) reported normal latency accompanied by unusual high square wave jerks during fixation and lower maximum period of fixation. Yang et al. (38) reported increased latency also in the MCI. Other studies reported pathological findings in some measures of the saccades, including a reduced peak velocity (39) or reduced gain (40). Garbutt et al. (41) reported reduced gain also in the supranuclear paralysis and in corticobasal degeneration. Anticipatory saccades were referred by Abel et al. (42) and Shafiq-Antonacci et al. (35). Other authors referred saccadic intrusions (34, 36) and Boxer et al. (36) claimed a correlation with the frontal tests. Other authors described altered anti-saccades (35, 36, 43-45); Boxer et al. (36) found the same alterations in the frontotemporal dementia, while Crawford et al. (43) referred normal anti-saccades in Parkinson's disease. Some authors indicated a correlation between pathological anti-saccades and the degree of dementia (43, 44); Crawford et al. (46) suggested a correlation with the spatial working memory and Peltsch et al. (45) with the Stroop test. On the other hand, Kaufman et al. (47) found no correlation with dementia and Heuer et al. (44) found normal values in the MCI. While studying more complex movements, authors suggested more frequent or longer fixation (40), diminished visual exploration (48), and decreased attention to the incongruous part of a figure (49).

In 1994, Scinto et al. (50) described marked hypersensi-

tivity in pupil dilatation response to Tropicamide, a cholinergic antagonist. This was confirmed by Grunberger et al. (51) yet not by others (52). Hypersensitivity was found only in the early-onset AD (53) or in other diseases (54). Pupilometry was used to identify a cholinergic deficiency and several alterations were found in the AD. Tales et al. (55) referred reduced amplitude of the pupillary constriction to light; Fotiou et al. (56) found an impaired pupillary light reflex, suggesting that an acceleration of the maximum constriction could be the best AD predictor. The same authors (56) found a correlation between maximum constriction velocity and maximum constriction acceleration with MMSE and Wechsler memory scale. Many authors examined the retina and with few exceptions (57), all agreed on reduced retinal fibre layer (RNFL) (58-60). A reduced RNFL was often found in the superior quadrant (58-60). However, similar observations were also made in other CNS diseases (61). Several authors have examined a possible association between glaucoma and AD. Tsilis et al.'s (62) meta-analysis was unsuccessful because the data were too heterogeneous to draw any conclusion. None of the following works brought to conclusive evidence: While some authors found a positive association (63) others claimed the opposite (64). Regarding glaucoma, several works showed morphological and functional changes in the visual and non-visual systems (65). The importance of these observations is currently debated; however, because these changes are also present in the early stages, their presence could be at least partially independent on raised intraocular pressure. Theoretically, several mechanisms can be common in these two diseases. Neurotoxicity has also been hypothesized: in vitreous samples, elevated tau and decreased amyloid levels were detected (66). Berdahl et al. (67) referred reduction of 3 to 4 mmHg in intracranial pressure in subjects with primary open angle glaucoma suggesting that the transluminal pressure gradient (the difference between intraocular and intracranial pressure) plays an important role in the genesis of the glaucoma. A meta-analysis (68) confirmed that higher transluminal pressure is related to structural glaucomatous changes. A link between age-related macular degeneration (AMD) and AD was also hypothesized given the many similarities between these two diseases as the presence of some molecular components i.e. β -amyloid and vitronectin, and complement activation (69). Several authors claimed a positive link (70), while others did not confirm this (71). In 2003, Goldstein et al. (72) referred a greater frequency of supra-nuclear cataract in AD; this finding was later confirmed in AD (73), Down syndrome (74) and transgenic animals (75). Some authors did not confirm this finding (76) while Lai et al. (77) found a greater frequency of cataract in Parkinson's disease.

4. Conclusions

Considering embryonal development, it is clear that the eye represents an optimal site for an early diagnosis of AD and for evaluating the effectiveness of the therapies. Several indications suggest an early involvement of the visual system in AD, yet this evidence remains inconclusive. The reason for this uncertainty is two folds. The first reason is the poor quality of the studies: Often the series are too small and the severity of the disease varies too widely to make a rigorous comparison possible. The second reason is that some alterations are not unique to AD, since they also occur in others degenerative CNS diseases. For example, α -synuclein and tau-pathology in the visual system was found in patients with AD and Parkinson's disease (20, 77). It is therefore possible to hypothesize that taupathies and some ocular diseases have common pathogenetic pathways. The identification of an AD-related ocular pathology might be a cheaper and easier diagnostic tool than the MRI or the lumbar puncture. However, this is also of theoretical importance because AD is usually regarded as a disease affecting cognitive status yet in the literature, several non-cognitive symptoms are described, such as motor, psychiatric or epileptic in the early stages or in the MCI (1). Recovering a metaphor used by Langston (78), it could be suggested that AD's cognitive symptoms might in fact only represent the tip of the iceberg.

Footnotes

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