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REVIEW ARTICLE

Use of Pupillometry in Dementia: A Review of Published Literature

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ABSTRACT

Introduction: Diagnosis of Alzheimer's disease is based on clinical symptomatology supplemented with neuroimaging findings. While there are invasive techniques like lumbar puncture and expensive techniques like positron emission tomography/single photon emission computed tomography (PET)/SPECT imaging available for diagnosis, none of these are totally accurate. Thus, there is a need for a cheap and noninvasive technique for diagnosing Alzheimer's dementia. Pupillary light reaction or pupillometry is one such technique based on the hypothesis that the pupillary size and reaction are governed by the cholinergic system of the brain, which is deficient in Alzheimer's dementia.

A review of the studies showed that pupillary measures have been studied in patients with or without mydriatic/miotic agents and in those receiving anticholinergic esterase medications. These studies are discussed in detail in this review.

Keywords: Alzheimer's disease, Light reaction, Parkinson's disease, Pupillometry.

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INTRODUCTION

Dementia is a clinical syndrome characterized by "global deterioration of mental functioning in its cognitive, emotional and conative aspects." The global annual incidence of dementia is estimated to be around 7.5 per 1000 population. The global prevalence of dementia in those aged more than 60 years is 3.9%, with the regional prevalence being 1.6% in Africa, 3.9% in Eastern Europe, 4% in China, 4.6% in Latin America, 5.4% in Western Europe, and 6.4% in North America.[1] Its prevalence almost doubles every 5 years after the age of 60 years, from approximately 1.5% in persons aged 60 to 69 years to 40% in those aged 90 years or more.[2] Definitive diagnosis of Alzheimer's dementia (AD) is only possible postmortem where brain biopsy shows cortical atrophy, amyloid plaques, and neurofibrillary tangles. In the antemortem state, the combination of clinical features and neuroimaging gives a diagnosis of probable Alzheimer's disease, once reversible causes of dementia have been excluded. Cerebrospinal fluid tau estimation and PET scans have a sensitivity of 73 to 100% and 80 to 100% respectively (Gaugler 2013).[3] They are invasive and/or expensive investigations to undertake. Another issue in treating AD is that only half the patients prescribed anticholinergic medications (acetylcholinesterase inhibitor, AChEI) respond to it.[4,5] As AcheEI therapy is expensive, especially for the low-income population of India, it would be useful for the clinician to identify patients who will respond best to before prescribing AChEI medications.

Thus, there is a need for sensitive investigation, which is also cheap and noninvasive, for diagnosing Alzheimer's disease.

RELATION OF ALZHEIMER'S DEMENTIA WITH PUPIL SIZE AND ITS REACTION TO LIGHT

The main etiology of AD is global shrinkage of the brain, consequent to which there is reduction in all the neurotransmitters, including acetylcholine (ACh). There is substantial evidence reporting a profound reduction of cortical choline acetyltransferase and cholinergic neuronal loss in patients with AD. The pupils are supplied by the III cranial nerve directly from the brain, and their size and responsiveness are governed by the sphincter and the dilator muscles of the iris controlled by the parasympathetic (cholinergic supply) and the sympathetic (adrenergic supply) nervous systems respectively (Fotiou et al.,). The parasympathetic oculomotor system involves projections from the Edinger–Westphal nucleus in the midbrain through the third cranial nerve and ciliary ganglion, to the sphincter pupillae muscle surrounding the pupil. Neurotransmitter involved both at the ciliary ganglion and the sphincter muscle is ACh; the Edinger–Westphal nucleus is cholinergic in nature as well. This system produces reflexive constriction of the pupil during light exposure.[6]

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Table 1: Pupillometric indices

Resting or baseline pupil radius recorded after 2 minutes dark adaptation. It is also quantified as the average of the pupil diameter 100 ms prior to the photostimulation
Latency of response is defined as the onset of pupil reaction to light. It is the time when the pupil has the maximum acceleration
Minimum pupil radius/peak constriction amplitude/minimum amplitude/maximum constricted size of pupil refers to the lowest pupil diameter after pupil reaction to the exposure to a light stimulus
Response amplitude is the difference between baseline pupil radius and the minimum pupil radius after the pupil reaction to light
Percent constriction is the ratio between minimum pupil radius and baseline diameter
Response time refers to the difference between the time corresponding to the minimum amplitude and the time corresponding to the light stimulus
Time for maximum constriction (T_{max}) is determined as the time when the constriction velocity is zero
Constriction velocity is defined as the ratio between response amplitude and response time
Maximum constriction velocity (VC_{max}) is the maximum rate of change in pupil diameter expressed in mm/sec over a given interval of time from initial size to maximal constricted size of pupil following stimulation by light as a consequence of introducing a dilute cholinergic antagonist to the eye. It is one of the most important indices that are significantly marking their presence in the diagnostic evaluation of AD
Maximum constriction acceleration (AC_{max}) is another important index in the prediction of diagnosis of AD
Time for maximum velocity is measured as depending on the empirically selected concentration of neural transmitter used and the amount of time before pupillary responses varies and may significantly differ for AD from normal population
Redilation velocity is defined as the rate of recovery expressed as mm/sec to maximal resting pupil radius after a photostimulation

As neurofibrillary tangles, which are a hallmark of Alzheimer's disease pathology, have been found in the oculomotor system of the Edinger–Westphal nucleus in patients with AD,[7,8] theoretically, index changes in the central cholinergic system will be associated with the disease progression, and the response to cholinergic treatment will be reflected in pupillary measures.

Thus pupillometry, which is a fast, cost-effective, noninvasive technique, can be potentially used to monitor the identification, progress, and response to treatment of Alzheimer's disease as a surrogate marker. In this article, we critically review the studies on using pupillometry in patients with AD, as well as present Indian data. The main pupillometric indices are described in Table 1.

STUDY DESIGNS

Most studies have used the cross-sectional design with single point assessment.[9-16] Comparative studies with AD included either two groups of patients with AD with or without AChEI treatment, or compared AD with healthy controls, other disorders with cognitive deficit, such as Parkinson's disease,[10,11] Down's syndrome,[17] or other dementias, such as vascular,[18] multiinfarct dementia,[19] or dementia with Lewy bodies.[20]

Pupillometric Measures in Alzheimer's Dementia

The studies on pupil parameters in AD can be broadly divided into two categories—those which have measured pupillary reaction without any topical mydriatic/miotic medication, or those which used either or both of these medications. These pharmacological actions of these drugs are on cholinergic system (as antagonists) or on adrenergic system (as agonists).

Studies not using Any Topical Agent

Granholm et al[11] showed that the maximal pupillary constriction (minimal amplitude) is more strongly correlated with cognitive deficit. Furthermore, VCmax and ACmax have been considered as the most sensitive indicators of cholinergic deficiency associated with Parkinson's disease (PD) and AD.[12] The ACmax and secondarily VCmax were the best predictors in classifying a subject as normal or as a PD patient with or without cognitive impairment,[10,21] while ACmax was the best predictor in classifying a subject as normal or as an AD with a perfect classification ability.[10,22]

Studies using Topical Mydriatic/Miotic Medications

Two agents have been used in the majority of studies: (i) Pilocarpine, a muscarinic agonist, which causes constriction of pupils by enhancing the cholinergic system, produced pupil constriction greater in AD patients as compared with normal controls;[23-25] (ii) cholinergic antagonist tropicamide which produces dilatation of pupils.

There is significantly greater dilation in AD patients with tropicamide 0.01% administered locally to the pupils, than in nonclinical controls.[17,26-30] In the study by Scinto et al,[26] a 13% increase in pupil diameter in response to tropicamide accurately identified 18 of 19 (95%) AD patients, whereas only 2 of 32 (6%) nonclinical controls exceeded this cut-off score. In another study,[31] a milder solution of tropicamide of 0.005% strength also produced similar changes, i.e., greater dilatation of the pupil in AD subjects. Iijima et al[18] tested both concentrations of tropicamide—0.01 and 0.005%—in subjects with AD and cognitively intact controls, the latter including nongeriatric subjects. In this study, the maximum pupillary dilatation was equal with tropicamide 0.01% between patients with AD and control subjects, but tropicamide 0.005% showed a difference in patients with AD, vascular dementia, and normals. Further, Scinto et al[26] showed

that those with "suspected" AD [which was assessed with memory and intellectual impairments (n = 5)] also showed exaggerated dilation responses, thereby signifying the use of tropicamide test as a measure to identify individuals in preclinical, early stages of AD.

Another prospective longitudinal study on community dwelling elders by Scinto[32] has shown that over a time period of 2 to 4 years, an exaggerated response on the pupil assay is a significant independent risk factor for developing preclinical AD, with an increased risk of four-fold. The study used discrete time survival modeling to assess the predictability of the pupil assay about a pattern of cognitive decline consistent with preclinical AD. When controlling for apolipoprotein E (ApoE) allele type, the odds ratio for pupil response as a risk factor increased to four.

In contrast, other studies have found considerable overlap between AD and control groups[30,33,34] Ferrario et al[35] found that 95% of normal controls showed similar dilation responses as patients with AD, and greater dilation in controls as compared to patients with AD. Nevertheless, a large amount of literature has found no significant difference in pupil responses.[19,34,36-44]

AChEI and Pupillary Reaction

Donepezil, an AChEI, is prescribed for treatment of AD, and works by inhibiting the breakdown of ACh, thereby increasing the available levels of this neurotransmitter in the brain. Fotiou et al[36] found that patients receiving donepezil had larger pupillary light reflexes in comparison with patients with AD, who were not receiving donepezil. Peak constriction amplitude (PCA) correlated significantly with dementia severity and donepezil treatment. Donepezil may partially normalize peak constriction latency (PCL) in patients with AD resulting in masked differences between normal controls and AD in PCL.

Whereas there is some evidence that donepezil may have partially blocked the effects of tropicamide on PCA, regardless of donepezil treatment, patients with AD differed significantly from normal controls in PCA.

Poor specificity has also been reported with comparable dilation responses in patients with AD and those with other types of dementia or neurological illnesses, such as frontotemporal dementia,[45] amnestic disturbances in alcoholics,[46] isolated memory deficiency,[39] intellectual impairments,[43] sporadic type of AD,[29] Down's syndrome,[17] extrapyramidal disorders,[30] progressive supranuclear palsy,[47] and multi-infarct dementia.[19]

Alzheimer's Disease vs other Neurological Disorders

Fotiou et al[36] examined tropicamide blockade of cholinergic oculomotor functions in AD, PD, and nonclinical controls. Tropicamide increased pupil diameter and reduced the amplitude and latency of the pupillary light reflex to a similar extent for all three groups. Although Scinto et al[26] found some specificity in AD, other researcher groups[28,48] found that tropicamide was not an effective diagnostic tool for AD in relation to Parkinson's disease, alcoholic dementia, and vascular dementia and proposed that it can be modulated by different gene dosage of ApoE 4.[19]

Indian Study

To the best of our knowledge, there is only one research report from India.[50] In this study, subjects aged 60 years or more with Diagnostic and Statistical Manual fourth edition diagnosis of AD and age-matched cognitively normal controls underwent pupillary assessment using tropicamide 1%. This study did not find any differences in pupillary measures with (at 5 and 15 minutes postinstillation) tropicamide 1% solution between AD and controls.

DISCUSSION

The AD has peripheral cholinergic deficit independent of the aging process. As pupillary light reflex is mediated through peripheral cholinergic system, and central cholinergic deficit in AD may indirectly result in peripheral cholinergic deficit, these patients could be expected to show increased sensitivity to tropicamide resulting in greater degree of pupillary dilatation. Reduced central inhibition of the Edinger–Westphal nucleus may also explain the pattern of results. Increased fatigue results in progressive miosis, especially in the dark, and larger PCA.[6]

Specificity of the PCA of the pupillary light reflex still can be put into discussion. Some studies found that as compared with normal controls, PD patients developed reduced PCA,[51,52] similar to AD patients.[36] The PCA, therefore, was sensitive to AD, but lacked adequate specificity. However, it is possible that the PCA deficits found in both are due to neuropathology in the Edinger–Westphal nucleus. Hunter[7] reported comparable neurofibrillary degeneration in the Edinger–Westphal nucleus in two PD cases and two AD cases, and found greater loss of neurons and gliosis in this nucleus in the patients with PD. Other possible explanation of reduced PCA in PD is that such patients may be less responsive to retinal dopamine amacrine cells that are involved in light adaptation.[51,53] Normal amacrine dopamine activity increases with increased retinal illumination. Hence, the hypoactivity of retinal dopamine cells in PD may contribute to reduced reactivity to illumination, and larger pupil size probably because of inappropriate dark adaptation.

Taken together, the studies on pupillometric measures present a contradictory picture. Most of investigations have used cross-sectional designs where it is difficult to assure that control groups are free of underlying AD pathology as there might be a possibility that subjects may have occult AD pathology prior to the manifestation of clinical symptoms. While markers of pathology may be positive, clinical signs of dementia can be absent. And thus, "normal" control sample can be contaminated as a comparison group.

Age, age of onset, and clinical characteristics of AD or ApoE could also serve as confounders.[17,49] Pupil dilation is more in patients and healthy controls with a greater number of alleles for ApOE4 gene,[48] and the 13% cut-point of pupil dilation was slightly better than the 15% cut-point when ApoE status was not controlled and both these cut-points were similar when it was controlled.[32] Hasegawa and Ishikawa[54] revealed that pupillary diameter decreases with advancing age, and the latency of pupil response to light is significantly prolonged in individuals above 60 years of age. This indicates weakening of autonomic supply (cholinergic deficit) of eyes with advancing age. However, larger pupillary dilatation with tropicamide is reported in older adults,[37,38,49] mostly in patients with AD and less than 70 years of age.[13,17]

Various environmental factors can also influence the sensitivity of pupillary size and reaction and may account for discrepant findings across studies.[11] The duration of pupillary contractions to light is a poor indicator of the intensity of the stimulus. However, the amplitude of the contractions may change from moment-to–moment, but it is sensitive to changes in stimulus intensity and reasonably repeatable in the same subject under the same conditions when a number of reactions are averaged. Background luminance can also influence the pupillary response for the class of neurotransmitters used in study. Constriction responses in bright light may neutralize dilation responses to tropicamide.

Similarly, dilation responses to darkness can supersede dilation responses to tropicamide. Loupe et al[41] found that the tropicamide test tended to be more sensitive to AD in the light than in darkness, but AD patients and nonclinical controls did not differ significantly in either the light or dark.

Furthermore, longer stimulus may overcome cholinergic deficits and trigger a more normal light reflex. The PCA deficits in patients with PD have been observed to be more severe in the 20-lux condition, and were less severe in the 40-lux condition, where PCA was abnormally reduced only at the earliest two time points. Patients with AD, in contrast, showed abnormally reduced PCA in both lux conditions at every time point. A PCA cut-off score of 1.24 mm best differentiated AD patients and controls, with 80% of AD patients correctly classified and 80% of controls correctly classified. Studies[12,36,55] that found reduced PCA used a brief (20–150 ms) light flash, whereas a 100 ms light stimulus used in one study did not find reduced PCA.[35]

Absorption of drug can be another confounding factor. Absorption is dependent on permeability of the cornea,[43,44] while cornea also has impacts from tears, blink rate, and contact lenses. Fitz-Simon et al examined ocular penetration of eye drops using fluorescein as a tracer and found that patients with AD and controls gave similar responses either in absorption of tropicamide or for pupillary dilation.

Dark colored eyes are also known to react less or more slowly to neurotransmitter agents as compared with lighter eyes, although this has not been consistently found in AD studies of tropicamide effects.[29,39,44] Gender showed strong correlations with measures of dilation in response to tropicamide for PD patients, suggesting women dilated less to tropicamide, but this correlation was in the opposite direction for AD patients and weak for controls, while some studies have not reported such effects.[29,37,38]

CONCLUSION

The pupil size and pupillary reaction to light have been shown to be related to the prediction of diagnosis and severity of dementia. Pupillary assay may be utilized in finding out dementia severity over time, predicting which patients are more likely to respond to treatment, change with response to treatment, and to determine when treatment is no longer impacting cholinergic systems and, therefore, may no longer be appropriate. However, the studies conducted until date do not support this aim. The studies are heterogeneous, mostly cross-sectional, and have used different patient groups and pupil assay techniques. An adequately powered controlled study utilizing contemporary standard diagnostic criteria for AD is required to establish the role of pupillometry in diagnosis and prognosis of AD.

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