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*Original Article*

# An image processing technique for diagnosis of Alzheimer's disease

*Massoud Mahmoudian*[*a], *Soltan Ahmed Ebrahimi*[a], *Zahra Kiani*[a]

## Abstract

**BACKGROUND:** Patients with Alzheimer's disease (AD) reportedly exhibit hypersensitivity to much diluted tropicamide solution (0.005%), a M4 muscarinic receptor antagonist. Therefore intraocular application of 0.005% tropicamide may be useful for screening dementia. The aim of this study was to simplify the pupil response test by using a new image analyzing system, which consists of a cheap, simple, and easy to use web-camera and a computer.

**METHODS:** Intraocular tropicamide of 0.005% concentration was administered in 3 groups: Alzheimer's disease patients (n = 8, average age = 76 ± 5), non-Alzheimer's disease elderly (n = 6, average age = 65 ± 7), and young subjects (n = 8, average age = 28 ± 5). Every 5 minutes for 60 minutes, image of the eye's shape were taken, and the diameter of the pupils was measured.

**RESULTS:** The results showed that differences in pupil dilation rate between Alzheimer's disease and non-Alzheimer's disease subjects were statistically significant. ROC analysis showed that after 35 minutes the sensitivity and specificity of the test were 100%.

**CONCLUSIONS:** Based on our results, we concluded that this recording system might be an appropriate and reliable tool for pupil response diagnosis test of Alzheimer's disease.

**KEYWORDS:** Alzheimer's Disease, Tropicamide, Pupil.

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More than 55 illnesses are associated with the development of dementia and Alzheimer's disease (AD) is the most prevalent form. Vascular dementia (VD) is the second most common form of dementia.[1,2] In 2006, the worldwide prevalence of AD was 26.6 million cases, and it was predicted that it will grow to 106.8 million in 2050. Among these, there were 12.6 million cases in Asia (48% of worldwide prevalence), and it was predicted that it will grow to 62.85 (59% of worldwide prevalence) in 2050.[3]

The development of reliable methods to establish a targeted diagnosis at the earliest stage is essential to improving prognosis of the disease, and establishing appropriate care and treatment.[2,4]

In 1994 Scinto et al reported that AD patients exhibited hypersensitivity to intraocular administration of very dilute tropicamide (0.01%) solution but there was some overlap between AD group and control subjects. Tropicamide is a muscarinic receptor antagonist drug that is used in ophthalmology at concentration of 0.5, and 1% to dilate pupil and cause relaxation of sphincter muscle of pupil.[5]

After this report, many researchers performed pupil dilation test and ten of them replicated Scinto et al results,[6] while others stated that there was no significant difference between AD and non-AD groups.[7]

Iijima et al in 2003 re-evaluated the pupillary test with 0.005% tropicamide, and claimed that there was not any overlap between AD patients, vascular dementia, and normal subjects.[6]

Pupilometery test for AD must be done in an ophthalmology office, and it is expensive. In

[a] Razi Institute for Drug Research, Department of Pharmacology, Iran University of Medical Sciences, Tehran, Iran.
* Corresponding Author
E-mail: masmah99@iums.ac.ir

this study, we performed the pupillary test with 0.005% tropicamide, in AD and non-AD subjects by using a new, simple and cheap image recording system consisting of a web-camera and a computer. The main aim of this study was evaluation of the ability of this new system to selectively identify AD subjects.

## Methods

### *Image Recording Device*

In this experiment, a web-camera (JVC), connected to a laptop computer was used. Images were captured and analyzed using Adobe Photoshop software (Adobe Inc). This system could take a high resolution image of the eye, so the pupil and iris diameter measurements were possible.

### *Procedures*

Alzheimer's patients were selected after the Alzheimer's Disease Caregive's Questionnaire (ADCQ) test. Three groups including non-AD elderly (n = 6, average age = 65 ± 7), young (n = 8, average age = 28 ± 5), and AD subjects (n = 8, average age = 76 ± 5) were used to study pupil dilation in response to tropicamide at 0.005% concentration. Participants were recruited from Iran Alzheimer's Disease Association.

Before the test, written informed consent was obtained from all patients. Participant with glaucoma and other eye diseases were excluded from the test. All AD patients were previously diagnosed by imaging procedures including MRI or SCAN, and neuropsychological tests based on DSM-IV criteria.

Tropicamide solution of 0.005% concentration was prepared just before each test. Before the test, the images of the eyes were taken as rest pupil size, and then one drop of 0.005% tropicamide was administered to one eye of each subject, while one drop of normal saline solution was administered to another eye. The images of the eyes were taken every 5 minutes for 60 minutes after drug administration. The images were stored in computer memory for future analysis (Figure 1). Pupil and iris sizes were measured, using Photoshop software (Figure 2). The ratio of pupil size to iris size before drug administration was expressed as 100%. The graph of percent changes in pupil size versus time after drug administration was plotted.

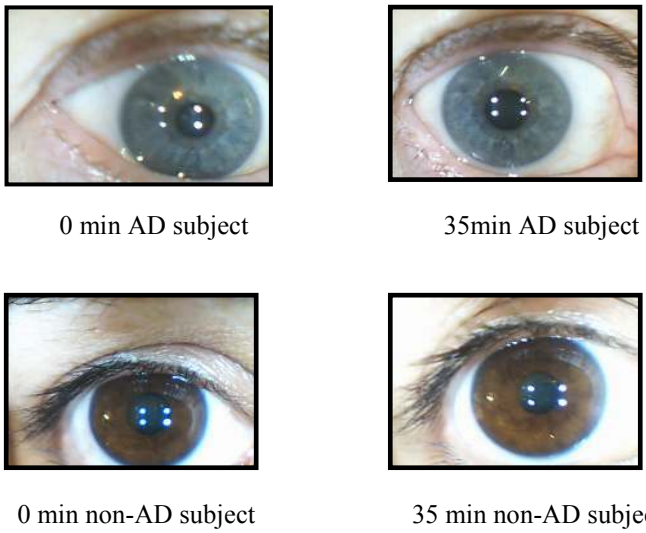



**Figure 1.** Representative images of the AD patient's (higher) and non-AD patient's (lower) iris before and 35min after the administration of 0.005% tropicamide

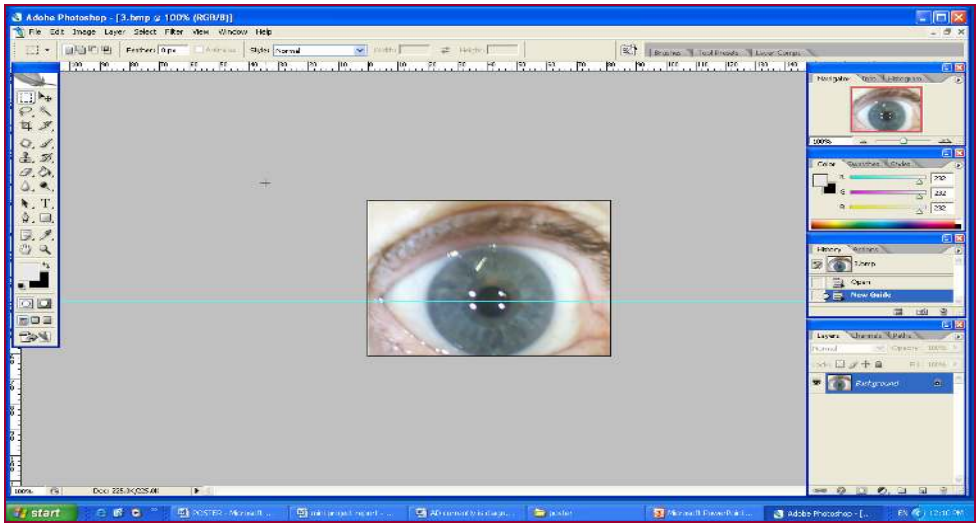


**Figure 2.** Measurement of pupil and iris size with adobe Photoshop software

## Results

Average change of pupil size (in percent) for each group is shown in figure 3. In this graph, x values represent percentage of change in pupil size after intraocular administration of 0.005% tropicamide, and saline solution, while y value represents time (min) after drug administration.

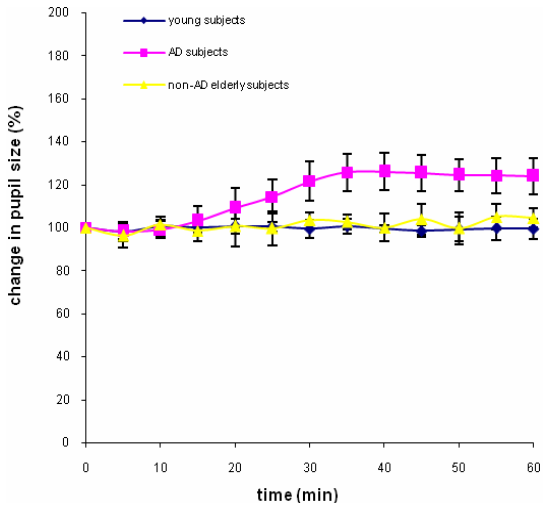



**Figure 3.** The changes of pupil size (%) after administration of 0.005% tropicamide versus time (min) were plotted. The three lines in this figure represent the average pupil size (treated eye) of young, AD, and non-AD elderly subjects respectively.

Saline administration had no effect and there were no significant differences between the three groups (data not shown). In AD subjects, pupil size gradually increased for about 35 min after 0.005% tropicamide administration. Administration of tropicamide had no effect on the pupil size in non-AD elderly or young subjects who showed no significant difference (one-way ANOVA [F (2, 19 = 38.4231, P < 0.001)]) (Figure 4).

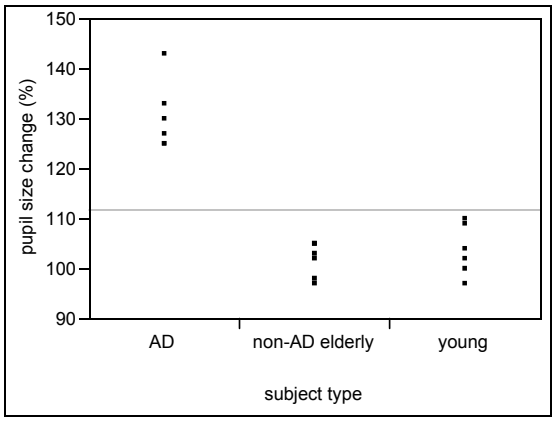



**Figure 4.** One-way ANOVA Analysis of pupil size change (%) by subject types

ROC analysis (Figure 5) showed after 15min, the test was not able to distinguish between AD and non-AD subjects (specificity = 0, sensitivity = 0). But at longer times after administration, both specificity and sensitivity

improved, such that after 25 min, the test was able to detect more than 60% of the AD patients with about 25% false positives. After 30 and 35 min, with a cut-off of 110% pupil dilation, the test detected 100% of the AD patients (sensitivity = 1) and had no false positives (specificity = 1).

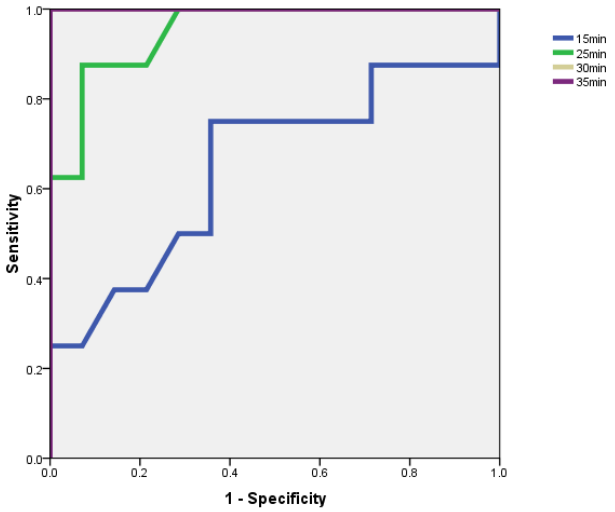



**Figure 5.** ROC curve: The most effective cut-off point for 0.005% tropicamide was computed on the graph and shown to be a pupil dilation rate of 110%. The lines representing 30 minutes (yellow) and 35 minutes (purple) are superimposed and only the purple line is visible.

## Discussion

Iijima et al had previously shown that measurement of pupil dilation after administration of 0.01% to 0.005% tropicamide, could be used to diagnose AD at an early stage and also distinguish AD from vascular dementia.[7] They also claimed that the test had a sensitivity of 1, i.e. detected all AD patients and a specificity of 1, i.e. had no false positives.

Some researchers have done pupil test to demonstrate possible mechanism of pupil hypersensitivity to very dilute tropicamide solution. Scinto et al assumed that loss of central cholinergic neurons in edinger-westfal (EDW) nucleus of cranial nerve III that is involved in control of pupil size, in early stages of AD participated in hypersensitivity to tropicamide. ApoE allelic variability is linked to pupil dilation, because it influenced on tau-hyperphosphorylation. Tau-based cell loss in EDW leaded to pupillary dilation in elderly who are clinically silent but have early pathology.[6,8]

Hou et al suggested that pupil size was controlled by the balance of the sympathetic dilation and parasympathetic constriction, and very dilute tropicamide induced pupil dilation in AD might be due to loss of function of noradrenergic neurons of locus coeruleus (LC) in brain stem.[9]

The test used by Iijima et al, however, used a sophisticated ophthalmology examination table which is usually not present in neurological surgeries. The aim of this study was to test a simple system, consisting of a webcam and a personal computer with commercially available software for use in diagnosis of AD.

Using this simple system, only AD subjects exhibited pupil dilation in response to 0.005% tropicamide which is a similar to Iijima et al findings.

ROC analysis of the data using a cut-off value of 110% showed that 35minutes after the administration of tropicamide, only AD patients showed enlarged pupils and under these conditions the system could detect all AD patients with no false positives. This is similar to what Iijima et al have found but with a system which is cheaper and more simple and can be used by every physician in his or her clinic.

## Conclusions

This simple and cheap imaging system can be used to detect Alzheimer's dementia and the fact that it does not need ophthalmology examination equipment, we suggest it can be used, along with other methods for the diagnosis of Alzheimer's disease.

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## Conflict of Interests

Authors have no conflict of interests regarding this work with any person or institution.

## Authors' Contributions

The original idea of using a web cam for the test was put forward by MM. The conversion of an ophthalmology examination table for measurement of pupil diameter using a CCD camera was carried out by SAE. This table was used as control to check the measurements made by the web cam. ZK carried out the measurements, prepared the results and drafted the early versions of the manuscript**.**

All authors have read and approved the content of final manuscript.

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