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*Original Article*

# Sensitive Pupil Response of Early-Onset Alzheimer's Patients to a Dilute Mixture of Cholinergic Antagonist and α -Adrenergic Stimulant

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## Abstract

**To investigate possible differences in pupil dilation and light reflex in Alzheimer's disease patients that can be attributed to the age of onset of the disease, a statistical comparison was made of pupil dilation and light reflex among early- and late-onset Alzheimer's disease, Down syndrome, and patients with vascular dementia, and normal controls. The subjects included 53 probable Alzheimer's disease outpatients, including both early-onset type (AD: n=21) and late-onset type (SD: n=32). They were compared with normal controls (n=15), Down syndrome patients (DS: n=6), and patients with vascular dementia (VD: n=9). All subjects and controls were dark-eyed Japanese. Pupil dilation and light reflex were tested in 21 AD and 32 SD patients, and were compared with those in the control subjects; 6 DS and 9 VD patients. The measured maximum increase in pupil diameter after instilling a mixture of anticholinergic and α-adrenergic stimulating drugs (Midrin-P®), in one eye was significantly greater in AD and DS than in the controls. However, there was no difference among SD, VD, and controls, suggesting a stronger pupil response to these drugs in AD than in SD. Pupil movement in response to light became significantly smaller and faster after instillation of the drugs in Alzheimer's disease patients. The above findings may be useful for the early detection of Alzheimer's disease.**

**Key words:** Alzheimer's disease, Down syndrome, pupil, tropicamide, light reflex

## Introduction

In 1994, Scinto et al.[1] reported a hypersensitivity in pupil dilation response among Alzheimer's disease patients (ALZ) to the cholinergic antagonist tropicamide. They used a change in pupil diameter of 13% as a cutoff point to distinguish between ALZ and non-Alzheimer's disease subjects. However, follow-up confirmation has been insufficient, and the results in later retrials by other researchers have varied[2-5].

This is especially true for Japanese and others who share the racial characteristic of dark eyes. Recently, Kardon[6] has argued that the use of a topical mydriasis test will not be a clinically useful diagnostic test for Alzheimer's disease because of the great individual variations in response. However, almost none of the papers reviewed by Kardon[6] examined the differences between early-onset (AD) and late-onset (SD) Alzheimer's disease.

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Based on a slightly modified version of one of the protocols of Scinto et al., we therefore studied the effectiveness of this method in distinguishing between controls and ALZ patients among Japanese, as well as the difference in pupillary response between early-onset Alzheimer's disease patients (AD) and late-onset Alzheimer's disease patients (SD). A letter describing the present research in part, is now in press elsewhere[7].

The NINCDS-ADRDA Work Group reported that, for research purposes, classification of ALZ should specify features such as onset before the age of 65[8]. The International Classification of Diseases-10 (ICD-10) classifies ALZ into early- and late-onset subtypes. The early-onset subtype generally appears before the age of 65.

This attempt to compare the difference between early- and late-onset Alzheimer's disease patients finds support in recent suggestions of an association between meiotic chromosome 21 non-disjunction (Down syndrome: DS), and AD[9,10]. Pathologists base a definitive diagnosis of ALZ on the amount of senile plaque and neurofibrillary tangle in the brain. DS has a similar pathohistology, and shares common neurobiochemical impairments in the choline and noradrenalin systems with ALZ [11]. It has been reported by several researchers[12-14] that among DS

patients there is a hypersensitive pupil dilation in response to cholinergic antagonists. We therefore chose DS patients as one of the reference groups for comparison of responses.

To rule out the possibility that it is dementia itself, and not specifically Alzheimer's disease, that causes dilation we included patients with vascular dementia (VD) as one of the subject groups. We also attempted to determine whether ALZ patients have a different constriction and recovery time to a light stimulus than do controls after dilation due to a mixed solution of a cholinergic antagonist and $\alpha$-adrenergic stimulant. If the hypersensitivity in pupil dilation response found by Scinto et al. does indeed vary according to the age of onset of Alzheimer-type dementia, this could be used as important additional evidence in the early detection of this disease.

## Subjects and Methods

As shown in Table 1, subjects included 53 probable Alzheimer's disease patients (ALZ: 16 males, 37 females; 53-88 years old, mean age 72.4), including both early-onset type (AD: n=21, mean age=64.9 years) and late-onset type (SD: n=32, mean age=77.4 years). The subjects were compared with normal controls (7 controls for the AD group, mean age 57.9 years, and 8 controls for the SD group, mean age 76.0 years; all of whom were medication-free spouses of patients with Alzheimer-type dementia, and had normal scores on a dementia questionnaire test), Down syndrome patients (DS: n=6, mean age 35.8 years), and patients with vascular dementia (VD: n=9, mean age 74.2 years). Eight of the controls were men, and 7 were women. There were no significant differences in mean age between the ALZ subjects and the 15 controls ($p = 0.058$). All subjects and controls were dark-eyed Japanese. Since gender has been shown to be insignificant in pupil size[15), 16)], the subjects were not classified by sex.

Diagnoses of dementia were in accordance with DSM-III-R [17)] and NINCDS-ADRDA[8)] clinical criteria, and were conducted by a specialist in geriatric medicine. Trisomy of chromosome 21 had been confirmed in all DS patients. All VD patients had multiple infarction-type vascular diseases, and none had major visual problems.

For all AD patients, onset of the disease was at 65 years of age or younger. The degree of dementia was determined for all 62 dementia patients by the Hasegawa Dementia Scale Revised (HDS-R), a scale for cognitive function[18)]. Scores on this scale have a high correlation coefficient of 0.94 with the Mini-Mental State Examination[18)]. It is one of the most commonly used screening tests for dementia in Japan. All 15 of the normal controls in the present study received full points on the HDS-R (Table 1).

Informed consent was obtained from all patients or their families. Cranial CT scans and MRI tests were performed on all dementia patients. All AD, SD, and VD patients underwent blood tests (erythrocyte count) and serum biochemical analysis. Subjects with abnormalities which could influence pupil size or light response and those with suspected mixed-type dementia were excluded[19)]. No subjects were taking cholinergic antagonists.

The method used for measurements of pupil diameter was similar to that used by Scinto et al.[1)]. While maintaining a relaxed atmosphere, the subjects were given a minimum of 10 min to adapt to a quiet, semi-dark room of 10 lux, after which their light reflex was measured. Next, one drop of a mixed solution of 0.01% tropicamide and 0.01% phenylephrine HCl (Midrin-P®,

**Table 1 Comparison of pupil dilation in Alzheimer's disease (ALZ) patients and in controls. (Mean ± Standard deviation)**

| Group | Solution instilled | ALZ patients | Controls | p |
|---|---|---|---|---|
| n (n of female) | | 53 (37) | 15 (7) | |
| Years of age | | 72.4 ± 7.8 | 67.5 ± 11.0 | 0.058 |
| HDS-R score | | 14.3 ± 7.9 | 30.0 ± 0.0 | < 0.001 |
| Pupil diameter | M | 5.11 ± 0.96 | 4.68 ± 0.97 | 0.139 |
| before instillation (mm) | S | 5.14 ± 0.85 | 4.57 ± 0.66 | 0.020 |
| p (M vs. S, paired *t*-test) | | 0.676 | 0.548 | |
| Maximum pupil diameter | M | 5.89 ± 0.90 | 5.19 ± 0.78 | 0.009 |
| after instillation (mm) | S | 5.37 ± 0.85 | 4.70 ± 0.61 | 0.006 |
| p (M vs. S, paired *t*-test) | | 0.003 | 0.075 | |
| Maximum increase of | M | 0.78 ± 0.57 | 0.51 ± 0.78 | 0.146 |
| pupil dilation (mm) | S | 0.23 ± 0.41 | 0.14 ± 0.41 | 0.440 |
| p (M vs. S, paired *t*-test) | | < 0.001 | 0.101 | |

M: Mixed solution of 0.01% tropicamide and 0.01% phenylephrine HCl,
S: Saline
The right column shows p values for ALZ patients vs. controls using Student's t-test.

**Table 2 Comparison of pupil dilation among early-onset type Alzheimer's disease patients (AD), Down syndrome patients (DS) and controls 69 years of age or less. (Mean ± Standard deviation)**

| Group | | AD | DS | Controls | p |
|---|---|---|---|---|---|
| n (n of female) | | 21 (18) | 6 (2) | 7 (4) | |
| Years of age | | 64.9 ± 5.4 | 35.8 ± 5.6 | 57.9 ± 7.3 | < 0.001 |
| HDS-R score | | 15.0 ± 8.4 | — | 30.0 ± 0.0 | |
| Pupil diameter | M | 5.22 ± 0.76 | 4.85 ± 0.37 | 5.21 ± 0.68 | 0.527 |
| before instillation (mm) | S | 5.32 ± 0.74 | 4.86 ± 0.41 | 4.91 ± 0.47 | 0.203 |
| p (M vs. S, paired *t*-test) | | 0.423 | 0.889 | 0.428 | |
| Maximum pupil diameter | M | 6.23 ± 0.68 | 6.33 ± 0.79 | 5.41 ± 0.76 | 0.044 |
| after instillation (mm) | S | 5.66 ± 0.82 | 4.91 ± 0.77 | 5.09 ± 0.45 | 0.074 |
| p (M vs. S, paired *t*-test) | | 0.003 | 0.028 | 0.125 | |
| Maximum increase of | M# | 1.00 ± 0.57* | 1.49 ± 0.54** | 0.20 ± 0.75 | 0.003 |
| pupil diameter (mm) | S | 0.33 ± 0.34 | 0.05 ± 0.74 | 0.18 ± 0.39 | 0.384 |
| p (M vs. S, paired *t*-test) | | < 0.001 | 0.028 | 0.937 | |

M: Mixed solution of 0.01% tropicamide and 0.01% phenylephrine HCl, S: Saline
#Significantly different ($p = 0.003$) among the 3 groups with the mixed solution instillation.
*$p < 0.05$, **$p < 0.01$; significantly different from controls using the Tukey-Kramer multiple comparison test.
The right column shows p values for the comparison among the three subject groups using ANOVA.

**Table 3 Comparison of pupil dilation among late-onset type Alzheimer's disease patients (SD), patients with vascular dementia (VD) and controls 70 years of age or older. (Mean ± Standard deviation)**

| Group | | SD | VD | Controls | p |
|---|---|---|---|---|---|
| n (n of female) | | 32 (19) | 9 (7) | 8 (3) | |
| Years of age | | 77.4 ± 4.7 | 74.2 ± 3.4 | 76.0 ± 4.4 | 0.066 |
| HDS-R score | | 14.1 ± 7.6 | 16.3 ± 5.6 | 30.0 ± 0.0 | < 0.001 |
| Pupil diameter | M | 5.03 ± 1.05 | 4.55 ± 0.64 | 4.22 ± 0.94 | 0.137 |
| before instillation (mm) | S | 5.02 ± 0.89 | 4.63 ± 0.74 | 4.27 ± 0.67 | 0.169 |
| p (M vs. S, paired *t*-test) | | 0.924 | 0.351 | 0.763 | |
| Maximum pupil diameter | M | 5.67 ± 0.94 | 5.23 ± 0.67 | 5.00 ± 0.74 | 0.213 |
| after instillation (mm) | S | 5.18 ± 0.80 | 4.68 ± 0.50 | 4.37 ± 0.54 | 0.062 |
| p (M vs. S, paired *t*-test) | | < 0.001 | 0.014 | 0.003 | |
| Maximum increase of | M | 0.64 ± 0.52 | 0.68 ± 0.33 | 0.78 ± 0.70 | 0.683 |
| pupil diameter (mm) | S | 0.16 ± 0.44 | 0.05 ± 0.42 | 0.10 ± 0.43 | 0.807 |
| p (M vs. S, paired *t*-test) | | 0.001 | 0.012 | 0.023 | |

M: Mixed solution of 0.01% tropicamide and 0.01% phenylephrine HCl, S: Saline
The right column shows p values for the comparison among the three subject groups using ANOVA.

**Table 4 Comparison of light reflex among Alzheimer's disease (ALZ) patients and controls. (Mean ± Standard deviation)**

| Group | | Solution instilled | ALZ patients | Controls | p |
|---|---|---|---|---|---|
| n | | | 18 | 14 | |
| Years of age | | | 69.1 ± 7.2 | 66.9 ± 7.7 | 0.412 |
| Maximum increase of | | M | 0.90 ± 0.65 | 0.79 ± 0.48 | 0.574 |
| pupil diameter (mm) | | S | 0.19 ± 0.34 | 0.08 ± 0.34 | 0.364 |
| p (M vs. S, paired *t*-test) | | | < 0.001 | = 0.001 | |
| CTI | Before instillation | M | 1417 ± 431 | 1833 ± 729 | 0.074 |
| (ms) | After instillation | M | 1151 ± 246 | 1712 ± 633 | 0.006 |
| | p# | | 0.007 | 0.213 | |
| | Before instillation | S | 1464 ± 342 | 1870 ± 783 | 0.089 |
| | After instillation | S | 1366 ± 183 | 1844 ± 864 | 0.062 |
| | p# | | 0.317 | 0.901 | |
| CR | Before instillation | M | 0.71 ± 0.04 | 0.72 ± 0.08 | 0.471 |
| | After instillation | M | 0.77 ± 0.05 | 0.78 ± 0.07 | 0.821 |
| | p# | | < 0.001 | 0.052 | |
| | Before instillation | S | 0.71 ± 0.05 | 0.73 ± 0.08 | 0.386 |
| | After instillation | S | 0.69 ± 0.05 | 0.70 ± 0.06 | 0.594 |
| | p# | | 0.252 | 0.289 | |

M: Mixed solution of 0.01% tropicamide and 0.01% phenylephrine HCl,
S: Saline
CTI: Constriction Time Index, CR: Constriction ratio
# Comparison before and after instillation
The right column shows p values for ALZ patients vs. controls using Student's t-test.

Santen Co., Ltd.) was instilled into the conjunctival sac of one eye of each subject, and as a control, one drop of physiological saline was instilled into the opposite eye. Pupil diameter was measured using video-adapted pupillography (Hamamatsu Photonics C 2514) every 5-10 min for 30 min with the subject gazing at a target 3 m distant. The maximum increase in pupil diameter (MIPD) was defined as the difference in pupil diameter directly before instillation and at maximum diameter. Light reflex was checked again at 40 min. A wide range of parameters were recorded, including constriction ratio (CR; the ratio between minimum diameter after the light and pre-light stimulus pupil diameter) and constriction time index (CTI; the time for the pupil to dilate to 63% of maximum dilation from 50% constriction). The results of these measurements were compared among all groups.

For statistical analyses, we used paired t-tests for comparisons of means of connected samples, such as between the mixed solution and saline; Student's t-tests for comparisons between patients and controls; one-way analysis of variance (ANOVA) to evaluate overall differences among the three subject groups; and the Tukey-Kramer multiple comparison test to evaluate differences between the means of pairs of groups. The $\chi^2$ test or Fisher's exact probability test was employed as needed for comparisons of proportional rate.

## Results

*Dilation*

Neglecting the age of onset, average MIPD in response to the mixed solution of 0.01% tropicamide and 0.01% phenylephrine HCl solution was 0.51 ± 0.78 mm for the 15 controls and 0.78 ± 0.57 mm for the 53 ALZ. They were not significantly (p = 0.146) different (Table 1). The dilation ratio was 13% or above (the reference value used by Scinto et al.) in 53.3% of the controls (8/15), and 60.4% of ALZ (32/53) (p = 0.768). The percentage of controls who had dilation ratios of 20% or above was 13.3% (2/15), compared to 34.0% for ALZ (18/53); again, which was not significantly different (p = 0.199).

Next, a comparison was made among the 3 younger groups of AD, DS, and controls under 70 years of age (Table 2). The maximal pupil diameter as well as MIPD was significantly greater after the mixed solution of tropicamide and phenylephrine HCl instillation than after the saline instillation in AD (p = 0.003) and DS patients (p = 0.028), but was insignificant in controls (p = 0.125). Overall MIPD differences among the 3 younger groups were significant (p = 0.003) with ANOVA. Using the Tukey-Kramer test, MIPD for the 21 AD patients was 1.00 ± 0.57 mm (p < 0.05) and that for the 6 DS patients 1.49 ± 0.54 mm (p < 0.01), both showing more dilation than the controls (0.20 ± 0.75 mm). The percentage of those with a dilation ratio of 13% or above was 42.9% (3/7) for controls, 66.7% (14/21) for AD, and 100% (6/6) for DS (p = 0.089). Comparing those with a dilation ratio above 20%, however, the percentages were: controls 0% (0/7), AD 42.9% (9/21), and DS 83.3% (5/6). The differences were significant between controls and either AD or DS (p = 0.009).

In the 3 older groups — SD (32 subjects), VD (9 subjects), and controls 70 years of age and above (8 subjects) — both the maximal pupil diameter and MIPD were significantly greater after the mixed solution of tropicamide and phenylephrine HCl

instillation than after the saline instillation in all 3 groups. Due to the influence of the drug on pupil dilation in controls, no significant difference in MIPD was seen among the 3 older groups (Table 3).

The mean HDS-R score for ALZ was 14.3 ± 7.9, for AD 15.0 ± 8.4, and for SD 14.1 ± 7.6. No significant correlation was seen between the MIPD and the HDS-R scores in any of the subject groups of ALZ ($r = -0.006$, $p = 0.968$) and AD ($r = 0.051$, $p = 0.826$).

*Light Reflex*

The light reflex of the subjects who received the mixed solution of 0.01% tropicamide and 0.01% phenylephrine HCl instillations was investigated by measuring CTI and CR. As shown in Table 4, data for only 18 ALZ subjects and 14 controls could be used after eliminating some data due to noise such as blinking. No significant change in CTI was observed between the values before and after the instillation of the mixed solution in controls ($p = 0.213$), but there was a significant shortening in ALZ patients ($p = 0.007$). CTI values after the mixed solution instillation were significantly shorter in ALZ subjects than in controls ($p = 0.006$). Similarly, no significant change in CR was observed between the values before and after the instillation of the mixed solution in controls ($p = 0.052$), but there was a significant change in ALZ patients ($p < 0.001$).

## Discussion

Differing from the report of Scinto et al., in which ALZ subjects had a mean age of 74 ± 7 years, we found a certain degree of overlap between ALZ subjects and controls regarding pupil dilation ratio. Growdon et al.[5] used similarly aged subjects; the mean ages of ALZ patients and control subjects were 74.5 ± 8.1 and 67.5 ± 8.2, respectively. In the present study, 53.3% (8/15) of the normal controls and 60.4% (32/53) of ALZ had pupil change greater than 13%. This difference was not significant ($p = 0.768$). Nor did a comparison of the percentage among the 3 younger groups (AD, DS, and under-70 controls) show a significant difference ($p = 0.089$). With pupil change of 20% or over, the difference in this rate between ALZ and controls was insignificant ($p = 0.199$). Only when a comparison of pupil change above 20% was made among AD, DS patients and under-70 controls, did AD (9/21) and DS patients (5/6) show a greater percentage with hypersensitivity ($p = 0.009$). A difference in iris color might be the cause of the different levels of pupil change between Scinto's paper and the present study. Other possibilities are that the drug used as well as other factors such as the difference in the subjects' ages were the influencing factors.

Among the AD, DS, and under-70 controls, MIPD was 0.20 mm in the controls and 1.00 mm in the AD patients, a significant difference ($p < 0.05$). The MIPD of DS patients, 1.49 mm, was also greater than that of the controls ($p < 0.01$). Among the 3 older groups (SD, VD, over-70 controls), in contrast, there was no significant difference ($p = 0.683$). There are many difficulties in obtaining suitable subjects for clinical study, especially in finding medication-free controls without any ophthalmological or neurological diseases. In the present study, the numbers of ALZ subjects and controls were few. The age matching among ALZ, AD, DS and controls was also incompletely formed. While admitting these drawbacks, the results of this study still amply demonstrate the new finding that there is a difference in pupil response between early-onset AD patients and controls.

These findings present the important suggestion that there is an age effect regarding pupil response to a mixture of tropicamide and phenylephrine HCl in ALZ patients. The difference in MIPD in only relatively younger groups indicates the possibility of using this as a supplementary test for the diagnosis of early-onset Alzheimer's disease. The finding that AD is similar to DS regarding pupillary response to the instillation of such a solution is quite interesting, in light of the hypothesis that they have a common causal mechanism.

Because of the slightly different solutions used, it may not be possible to make a direct comparison between this and the study of Scinto et al. in which a simple tropicamide solution was used. The phenylephrine HCl contained in the mixed drugs, used in the present study, is an $\alpha$-adrenaline receptor stimulant which constricts the dilatator muscle. We chose the mixed solution of 0.01% tropicamide and 0.01% phenylephrine HCl solution with the reasoning that it would perhaps more clearly show any difference between dementia patients and controls by augmenting the pupillary response.

The present results concerning light reflex showed significant differences in CTI and CR between those values before and after instillation of the mixed solution among the 18 ALZ subjects ($p = 0.007$ and $p < 0.001$, respectively). When the eyes were dilated in response to a very small amount of solution combining cholinergic antagonist and $\alpha$-stimulant, CTI was shorter in the ALZ patients than in the controls, although the intensity of the light and the initial pupil size were the same. This fact shows that, after instillation of such drugs, Alzheimer's patients have a shorter constriction and recovery time to a light stimulus from this dilated state.

The CTI and CR used for the light reflex were arbitrary indicators for this study, but several similar indicators have been used to date. Pozzessere et al. saw very little change between age and constriction time (from the end of the latency period to the maximal degree of meiosis) or half-redilation time (time needed for the pupil to reach half its basal value)[20]. Piha et al. reported that the relative reflex amplitude (RRA) was independent of age and sex[21]. The results of the present study revealed significant differences in CTI and CR between those values before and after instillation of the mixed solution of tropicamide and phenylephrine HCl among ALZ patients, but we were unable to investigate the extent of these effects by age group. Considering the fact that a significant difference was seen only between the MIPD in the early onset AD patients and in the controls, it may, in the future be possible to use CTI and CR as new indicators, or, perhaps better, in combination with MIPD as a supplementary diagnostic method for early onset AD.

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