PUPIL REACTIVITY IN ALZHEIMER'S DISEASE - A REAPPRAISAL .

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Purpose. To study the mechanisms responsible for the hyper reactivity of pupil size to cholinergic antagonist tropicamide in Alzheimer's disease.

Methods. Resting pupil size and pupil light reflex and their evolution after topical instillation of 0.01% tropicamide were studied in 20 Alzheimer's patients and 20 age matched controls. Pupil diameter was quantified with a near-infrared photo-oculometer.

Results.

The initial pupil diameter was significantly smaller in Alzheimer's (4.61 mm for controls versus 4.33 mm for Alzheimer's, $p = 0.074$). 30 minutes after instillation of tropicamide, the diameter of the instilled pupils reached identical levels (5.05 mm for controls, 5.06 mm for Alzheimer's, $p = 0.87$). There was no significant difference in the latency of the pupillary light reflex (305.6 msec for controls, 309.4 msec for Alzheimer's, $p=0.56$).

Conclusions. The reduced initial pupil size and the normal latency of the pupillary light reflex are against the hypothesis of an altered parasympathetic pathway.

None

Introduction.

The hyper reactivity of the pupil to anticholinergic agent tropicamide has been proposed for the early diagnosis of Alzheimer's disease (AD) [1]. However, several recent studies question the applicability of this test on individual patients on the basis of its lack of specificity and sensitivity [2-7]. Possible causes for these problems may be related to uncontrolled parameters and a lack of understanding of the involved mechanisms.

In order to evaluate the mechanisms of the hyper-reactivity to anticholinergic agent, we first studied the absolute resting pupil diameter (PD) which is noted to increase when the efferent parasympathetic fibers to the iris are damaged by a lesion of the oculomotor nucleus or the third nerve [8]. We also studied the latency of the pupillary response to a light stimulus (PLR) as an index of the iris parasympathetic nervous system activity [9]. Studies of the effect of topical pharmacological agents on the pupil show that the responses are extremely dependent on the initial PD [10-11]. Unfortunately this parameter is not taken into account in previous studies of the pupillary responses to tropicamide in patients with AD [1-7] which used only relative variations of the PD. This raises the possibility that variations of the initial PD are one of the causes of the reported low sensitivity and specificity of this test. To answer this question, we studied the absolute pupillary responses to tropicamide and analyzed the influence of the initial PD on these responses.

Methods.

We studied 20 patients diagnosed with probable or possible Alzheimer's disease on the basis of NINCDS-ADRDA criteria [12] and a control group of 20 elderly subjects without memory complaint and cognitive impairment disclosed on a clinical interview and an MMS score higher than 26/30. Both groups were age and sex matched. Patients with AD were 12 men and 8 women aged 50 to 87 years (average 68.5). Controls included 13 men and 7 women aged 59 to 81 years (average 67.0). Subjects receiving topic eye drops or pupil active agents or tacrine were excluded as well as subjects with intraocular hypertension, glaucoma or severe cataracts.

The pupil diameter was determined as the average of 300 measurements from a video based near-infrared pupillometer (Metrovision, Villeneuve d'Ascq, France) providing 60 measures per second. Each measurement was based on the diameter of the circle providing the best fit with the pupil contour. Subjects were seated in a dimly lighted room (luminance of about 10 cd/m2). After 3 minutes, a first determination of the PD was made on each eye. It was followed by the recording of the PLR to a series of 6 to 8 flashes of light, each with a duration of 300 ms and a time interval of 2000 ms. Thereafter, one drop of freshly made tropicamide 0.01% was instilled in one eye and one drop of physiologic serum in the other eye. PD and PLR were recorded immediately after installation and every 5 minutes during the course of the next 45 minutes.

Results.

Resting pupil diameter. Figure 1 represents the evolution of the absolute pupil diameter for the instilled and non instilled eyes in the AD and control groups. These results show that the initial PD is significantly smaller in patients with AD compared to the control group (4.67 mm average PD for controls versus 4.30 mm for patients with AD, $p = 0.014$ for the t test).

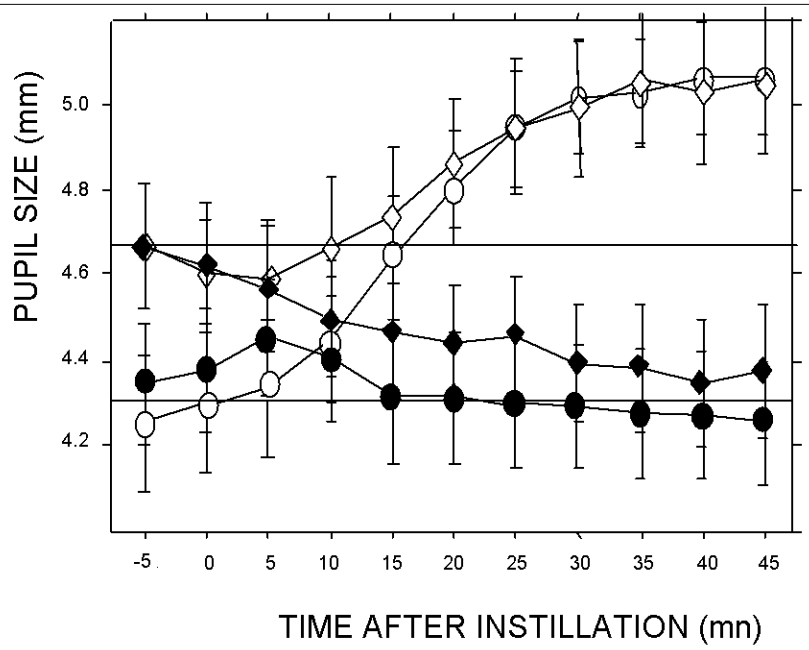

Figure 1

Evolution of the absolute pupil diameter after instillation of tropicamide (average plus and minus the standard error).

Diamond symbols are for the control group and circles for the group patients with Alzheimer's disease.

Open symbols are for the eye instilled with tropicamide and filled symbols for the non instilled eye.

The PD of the instilled pupil of the two groups reaches the same level after instillation (5.05 mm average PD for controls versus 5.06 mm for patients with AD, $p = 0.96$). In controls, there is a significant reduction of the PD of the non instilled pupil (- 0.29 mm average change, $p=0.0015$), opposite to the increase of pupil diameter of the instilled eye

(+ 0.38 mm average change $p < 0.0001$). In the AD group, there is no such change for the non instilled eye (-0.09 mm average, $p=0.21$) even though the change for the instilled eye is much larger than in controls (+ 0.81 mm average, $p<0.0001$).

A second analysis was performed to evaluate the effect of the initial PD on the pupillary response. Figures 2 and 3 represent the results obtained on groups of control subjects and patients with AD split according to their initial PD. Figure 4 provides a summary of the same data, showing pupil dilation 45 minutes after instillation versus the initial PD in control subjects and patients with AD.

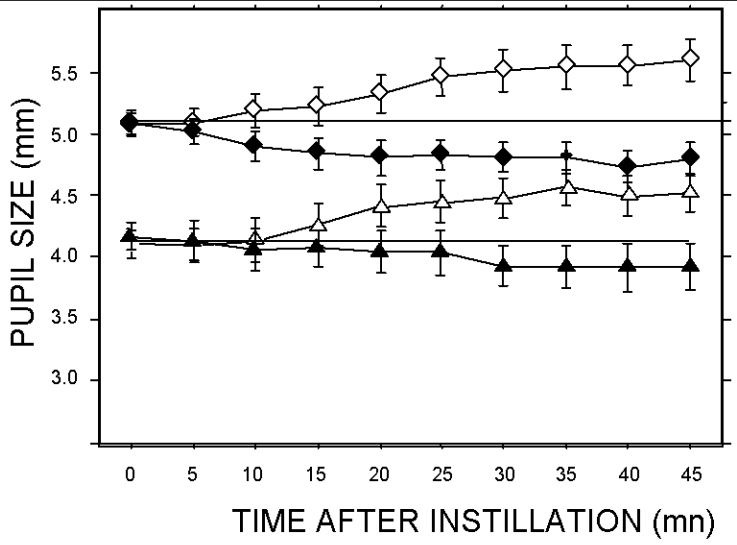

Figure 2.

Evolution of the absolute pupil diameter for 2 groups of control subjects split according to the initial pupil size (4 mm group = 3.5 to 4.5 mm, 5 mm group = 4.5 to 5.5 mm). Groups with less than 3 subjects are not displayed. Results are plotted as the average plus and minus the standard error. Open symbols are for the eye instilled with tropicamide and filled symbols for the non instilled eye.

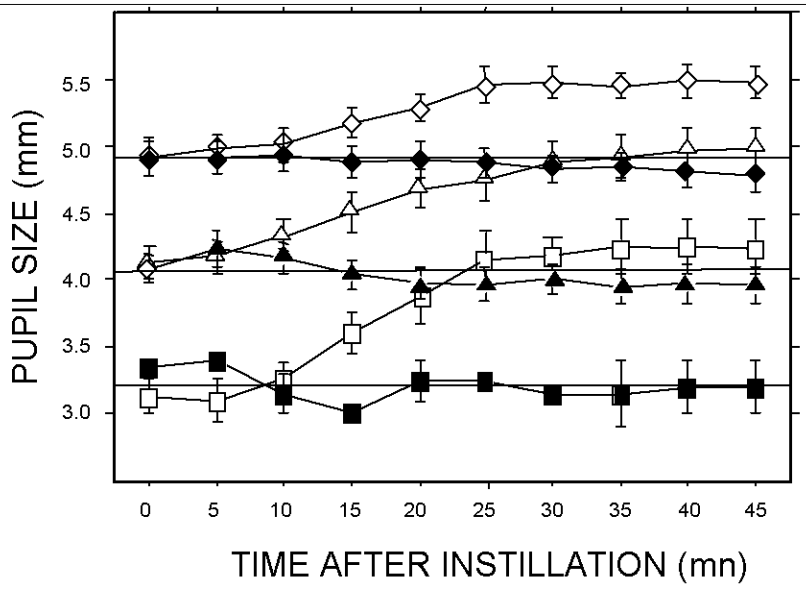

Figure 3.

Evolution of the absolute pupil diameter for 3 groups of patients with Alzheimer's disease split according to the initial pupil size (3 mm group = 2.5 to 3.5 mm, 4 mm group = 3.5 to 4.5 mm, 5 mm group = 4.5 to 5.5 mm). Groups with less than 3 subjects are not displayed. Results are plotted as average plus and minus the standard error. Open symbols are for the eye instilled with tropicamide and filled symbols for the non instilled eye.

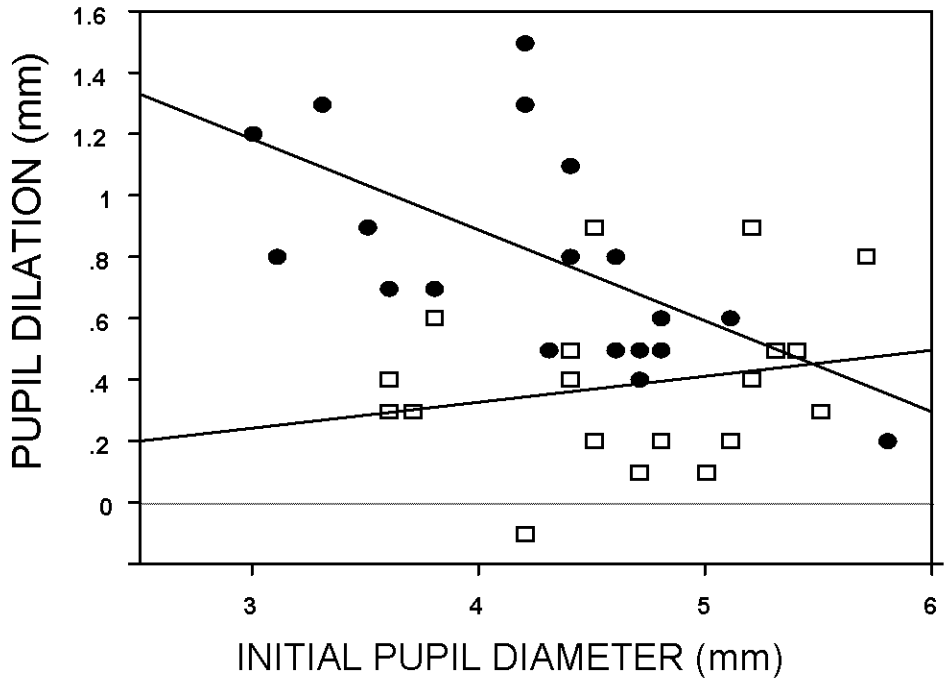

Figure 4.

Pupil dilation versus the initial pupil size of instilled eyes in patients with Alzheimer's disease (filled circles) and control subjects (open squares).

In patients with AD, the response is larger when the initial PD is smaller: 0.81 mm average for the 3 mm group, 0.77 mm for the 4 mm group and 0.20 mm for the 5 mm group). This trend is not found in controls (0.37 mm for the 4 mm group and 0.35 mm for the 5 mm group). The fact that the non instilled pupil constricts in controls and does not constrict in patients with AD is found to be independent of the initial PD. Therefore, the absence of constriction in patients with AD does not result from an initially smaller PD.

Pupillary light reflex. There is no significant difference in the latency of the PLR between the AD and control groups (before instillation : 326.8 ms for controls and 333.4 ms for patients with AD, p=0.36; 45 minutes after instillation : 318.7 ms for controls and 321.2 ms for patients with AD, p=0.82). There is no significant difference in the amplitude of the PLR (before instillation: .98 mm for controls, .89 mm for patients with AD, p=0.16; 45 minutes after instillation : .90 mm for controls, .82 mm for patients with AD, p=0.38).

Discussion.

Mechanisms. Our study allows us to draw some conclusions about the mechanisms involved in the hyper reactivity to tropicamide. The significant decrease of the initial PD and the absence of increased latency of the PLR in patients with AD rule out the hypothesis of a reduced innervation of the target muscle [1, 13]. The absence of difference of the PLR response after instillation between controls and patients with AD is not consistent with the hypothesis of an increased action of tropicamide resulting from differences in corneal permeability [13-14]. The fact that both responses to the antagonist, tropicamide and to the agonist, pilocarpine [13,15,16,17] are increased in patients with AD is another argument against a mechanism at the iris cholinergic receptor level [10,14]. One mechanism compatible with our results is lessening of central inhibition of the pupilloconstrictor nucleus as evoked previously by Lowenfeld [8]. Arguments in favor of such an hypothesis are the existence of sympathetic inputs from the central nervous system inhibiting the parasympathetic tonic mechanisms controlling pupil size at least in animals [18-19] and several reports of alterations of the sympathetic system in AD [20-21]. An additional finding is that the non instilled pupil does not constrict in patients with AD whereas, in control subjects, it shows a consensual response to light compensating the dilation of the instilled pupil. This seems to indicate that patients with AD present a specific alteration of the pupillary response to a sustained visual stimulus. The mechanisms of these alterations remain uncertain. Several studies suggest that pupil responses to transient and sustained stimuli are mediated by different visual channels [22-23]. Whether the alteration of the sustained response is related to alterations of the visual system described in patients with AD [24] cannot be answered from our data.

Effect of the initial PD . Our results indicate that the initial PD has an important effect on the pupillary response and consequently on the discriminability of the test. Patients with an initial PD lower than 3.5 mm were exclusively from the AD group. For the 4 and 5 mm initial PD groups, the discrimination between controls and patients with AD decreased as the size of the initial PD increased, from a p value of 0.002 for the 4 mm group to 0.03 for the 5 mm group. For the 6 mm group, control subjects and patients with AD could not be discriminated.

Sensitivity of the test. Our results provide some additional indications about the low sensitivity of some previous studies. The size of the pupil response is small (.81 mm average in patients with AD) and it can only be measured by a very sensitive technique, with a precise control of parameters such as ambient illumination. Another important parameter is the reference used for measurements of the responses. Some authors used the diameter of the non instilled pupil with the purpose of minimizing the influence of external factors affecting both eyes simultaneously. This is not a suitable approach given the presence of a compensatory constriction in control subjects and its absence in patients with AD. These effects reduce considerably the change in PD with respect to the non instilled pupil (mean difference in controls = .68 mm, in patients with AD = .81 mm, p=.34).

Finally, precise quantitative measurements of the response of the instilled pupil diameter with respect to its own initial PD does distinguish patients with AD from age matched control subjects when this initial PD is small (i.e. less than 5 mm in diameter).

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