·Clinical Research·

Characteristics of pupillo-accommodative functions according to time of onset, gender and age in tonic pupil

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Abstract

• **AIM: To evaluate the characteristics of pupillo-accommodative functions in patients with idiopathic tonic pupil according to the time of onset, gender, and age.**

• **METHODS: Totally, 15 males and 19 females were divided into 2 groups depending on the time of disease onset: group I (onset <2 months, *n*=20) and group II (onset >2 months, *n*=14). A supersensivity test was conducted by applying diluted pilocarpine 0.125% to the eye and accommodative functions were evaluated using the near-point of accommodation (NPA) as the cutoff point, at which the patient experienced blurred vision. Pupil size and the ratio of decrease in the affected pupil after instillation of 0.125% pilocarpine were investigated.**

• **RESULTS: There was no significant difference between the 2 groups regarding the various pupillary reflex results, including data on the affected pupil size before and after 0.125% pilocarpine, anisocoria, and ratio of pupil decrease. No significant difference in NPA was found between the 2 groups. However, female patients were noted to have greater anisocoria and a faster constriction ratio than those of the male patients (*P*=0.02 and *P* =0.04). On subgroup analysis, female patients from group II had larger affected-pupil sizes before 0.125% pilocarpine instillation and longer NPAs than those of the male patients.**

• **CONCLUSION: No relationship was found between time of onset and dysfunction of pupillo-accommodative functions. Pupillo-accommodative functions and age were not related, except for the NPA.**

• **KEYWORDS:** tonic pupil; accommodation; cholinergic supersensitivity
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INTRODUCTION

It is well known that tonic pupil is caused by damage to the postganglionic parasympathetic innervation of the intraocular muscles, which results in the characteristic syndrome [1]. The typical characteristics of tonic pupil are mydriasis, defects in accommodation, poor or absent light reflexes, and tonic near reflexes[2,3].

Tonic pupil is characterized by one or more of the following abnormalities: a poor pupillary reaction to light, possibly accompanied by a regional palsy of the iris sphincter; accommodation paresis; cholinergic supersensitivity of the denervated muscles; a pupillary response to near stimuli that is unusually strong and tonic; and pupillary redilation after constriction to near stimuli that is slow and tonic[1,4].

The characteristics of tonic pupil have been investigated previously in several studies. Cholinergic supersensitivity may also diminish over time, as reinnervation of iris sphincter segments by accommodative neurons occurs over the following 2-4 months [5]. Sectorial palsy is usually present throughout the course of the disease, from onset to recovery, although sensitivity to light varies, and accommodative functions are regained slowly [6]. However, this pattern of disease progress is not always presented in clinical cases. Thus, we evaluated and postulated pupil response with 0.125% pilocarpine and accommodative function, to enhance previous findings on the onset and symptomatic variances in idiopathic tonic pupils.

SUBJECTS AND METHODS

Subjects We evaluated 34 patients with unilateral idiopathic tonic pupil who had visited Kim's Eye Hospital (Seoul, Korea). This research study was reviewed and approved by the Institutional Review Board (IRB) of Kim's Eye Hospital. The following inclusion criteria were applied for selection of participants: presence of anisocoria with unilateral absence or a slow pupillary reaction to light, sectorial palsy of pupil, and normal ocular movement. Patients were excluded from the study if they had a previous history of vitreoretinal surgery or ophthalmic disorders, except for mild refractive errors and mild cataract. Eyes with secondary tonic pupil caused by preexisting systemic neurologic disorders, as well as eyes with retinal vascular disease, uveitis, glaucoma, and retinal

breaks were also excluded from the study. To analyze the characteristics of tonic pupil according to time of onset, the patients were divided into 2 groups: group I (onset <2 months, n=20) and group II (onset >2 months, n=10).

Methods Full ophthalmologic examinations were performed, including visual acuity, manifest refraction, slit-lamp examination and fundus examinations. Before any manipulations such as instillation of topical anesthetic, the size of the pupil was measured manually through slit-lamp examination in the room light by one author (USK). A supersensivity test was conducted by applying diluted 0.125% pilocarpine to the eye, which was prepared by diluting 1 part of 1% pilocarpine with 7 parts of hyaluronic acid solution, and the diameter of the pupil was measured after 30min. To evaluate the effects of 0.125% pilocarpine on pupil size, the constriction ratio was defined as [(pupil size before 0.125% pilocarpine instillation-pupil size after 0.125% pilocarpine instillation)/pupil size before 0.125% pilocarpine instillation]× 100% . Cholinergic supersensitivity was defined when the abnormal pupil constrict more than the normal one. Accommodative functions were evaluated using the near-point of accommodation (NPA) as the cutoff point, at which the patient experienced blurred vision.

Statistical Analysis All the data were recorded, and were analyzed using the Statistical Package for Social Sciences (SPSS; Chicago, IL, USA) program version 12. Descriptive results were expressed as percentages for categorical variables, and as means ±standard deviation (SD) for continuous variables. Student's t-test was used to analyze statistical differences of pupillo-accommodative function between groups. The correlation between age and pupillo-accommodative functions was analyzed using Spearman's nonparametric correlation.

RESULTS

To evaluate the effects of the onset time on pupil responses, we compared group I to group II. The mean ages were 38.5± 10.71 years in group I and 38.7±11.29 years in group II. The size of the affected pupil both before and after 0.125% pilocarpine instillation was not significantly different between the 2 groups (P=0.529 and P=0.583, respectively). Second, anisocoria, which was measured as the difference in size between the affected and healthy pupils, was not significantly different (group I: 2.12 ±1.59mm, group II: 1.83±0.96mm, P=0.515). Moreover, there was no difference in the constriction ratio (P=0.887), and the NPA also demonstrated no significant difference between the 2 groups (P=0.956, Table 1).

We then evaluated pupil differences according to gender, on the assumption that the pupil's responses and the NPA were not dependent on the time of onset (Table 2). In group II, pupil size before 0.125% pilocarpine instillation and the NPA demonstrated significant differences between male and female participants (P=0.008 and P=0.008, respectively); a larger affected pupil size before 0.125% pilocarpine and longer NPA were observed in the female patients. When all the participants were analyzed, female patients were observed to have a significantly greater anisocoria and a higher constriction ratio compared with male patients (P= 0.02 and P=0.04, respectively).

Finally, we analyzed the relationship between age and pupillo-accommodative function. Analysis of the NPA demonstrated a positive correlation (group I: 0.647, group II: 0.755), however, other factors including pre and post pupil size after 0.125% pilocarpine, anisocoria and decreased rate were not shown correlation with age (Table 3).

Table 1 Difference of pupillo-accommodative functions between groups

	Group I (n=20)	Group II (n=14)	P
Age (a)	38.5±10.71	38.7±11.29	0.405
M:F	10:10	5:9	[1]0.327
Mean time of onset (day)	22.3	272.5	<0.001
Pupillo-accommodative functions			
Pre size (mm)	5.70±1.08	5.46±1.01	0.529
Post size (mm)	3.76±1.06	3.57±0.89	0.583
Anisocoria (mm)	2.12±1.59	1.83±0.96	0.515
Constriction ratio (%)	32.0	32.9	0.887
NPA (cm)	12.4±4.51	15.1±7.38	0.956
Supersensitivity	6 pts (30.0%)	3 pts (21.4%)	[1]0.587

Pre size: Pupil size before 0.125% pilocarpine; Post size: Pupil size after 0.125% pilocarpine; NPA: Near point of accommodation. [1]Chi-square test.

DISCUSSION

The present study suggested that no relationship was found between time of onset and dysfunction of pupillo-accommodative functions; however, female patients were more susceptible to tonic pupil.

In this study, the age of onset (38.5 and 38.7 years in group I and II, respectively) was slightly lower than the mean age stated previously [1,4]. Results of the present study correspond well with those of an earlier study, which reported that, in Adie's syndrome, pupillary light reactions do not recover [1]. Thus, the loss of the pupillary light reflex also may be permanent in local tonic pupil. The cholinergic supersensitivity test is considered to be one of the signs of tonic pupil. Cholinergic supersensitivity may be present as early as 4-5d after the onset of acute denervation, and may diminish over time, owing to reinnervation of the iris sphincter segments by accommodative neurons. As stated previously, supersensitivity to diluted 0.125% pilocarpine (decreased ratio) should be greater in group I (where symptomatic onset occurred less than 2 months prior to the start of the study), since, in the chronic stage, the pupil does not respond to 0.125% pilocarpine. However, analysis of the decreased ratio showed no significant difference between the groups [7]. Leavitt *et al*[8] reported the pupillary responses to 4 different concentrations of pilocarpine in normal subjects. They concluded that normal pupils constrict in the presence of 0.125% pilocarpine, and therefore suggested that 0.0625%

Table 2 Characteristics of pupillo-accommodative functions according to gender

Parameters	Group I			Group II			Total		
	M	F	*P*	M	F	*P*	M	F	*P*
Age (a)	37.4±10.8	39.6±11.1	0.66	41.2±11.2	37.3±11.7	0.56	19.2±9.12	30.3±17.6	0.55
Pre size (mm)	5.57±1.20	5.84±0.99	0.59	4.64±0.65	5.98±0.83	0.008	5.26±1.12	5.90±0.90	0.84
Post size (mm)	4.12±0.68	3.37±1.29	0.15	3.22±0.74	3.77±0.95	0.28	3.82±0.80	3.57±1.12	0.15
Anisocoria (mm)	1.45±1.19	2.80±1.71	0.06	1.42±0.71	2.08±1.05	0.20	1.44±1.02	2.33±1.36	0.02
Constriction ratio (%)	23.2	41.7	0.07	30	34	0.64	25.6	38.3	0.04
NPA (cm)	20.6±9.99	34.1±20.9	0.14	16.3±8.0	26.0±13.1	0.008	12.5±5.12	14.1±6.40	0.51

Pre size: Pupil size before 0.125% pilocarpine; Post size: Pupil size after 0.125% pilocarpine; NPA: Near point of accommodation.

Table 3 Correlations between age and pupillo-accommodative functions

Parameters	Group I	Group II	Total
Pre size	-0.02	-0.187	-0.272
Post size	-0.202	-0.074	-0.133
Anisocoria	0.226	-0.39	-0.125
Decreased ratio	0.021	-0.359	-0.162
NPA	0.647[a]	0.755[a]	0.646[a]

[a]$P<0.05$ *vs* others. Pre size: Pupil size before 0.125% pilocarpine; Post size: Pupil size after 0.125% pilocarpine; NPA: Near point of accommodation.

pilocarpine can be used to distinguish a pupil with Adie's syndrome from a normal pupil. Unfortunately, we used a concentration of 0.125% pilocarpine based on previous study methods [7]; this might be the reason no significant change was observed between the 2 groups. In addition, chronic tonic pupils are often smaller in the room light compared to the fellow normal pupil. This might be another contributing factor to finding no differences between the 2 groups. The onset time may not have been exact in this study, owing to the patients determining their own time of onset, which may have resulted in the similar degree of supersensitivity in the 2 groups-this is a major limitation of the study. Therefore, the use of 0.125% pilocarpine in this study meant that supersensitivity could not be detected, or that the supersensitivity could not recover and was prolonged. Furthermore, the difference in the NPA between the 2 groups was not significant suggesting that the time of onset is not related to improvements in the NPA.

When gender differences were analyzed, the results were shown to be significant. First, compared with male patients, female patients in group II had a larger affected pupil before 0.125% pilocarpine instillation and longer NPA (chronic stage of the disease). Second, in both groups I and II, female patients were observed to have larger anisocoria and higher constriction ratio. This suggests that the degree of pupillo-accommodative dysfunction could be greater in female patients. It is well known that tonic pupil is associated with autoimmune disease, and a large number of autoimmune diseases are more prevalent in women [9-11]. Quintero *et al*[12] suggested that prevalence could be related to hormonal changes and genetic factors, which might explain the results observed in female patients. However, unfortunately, we did not investigate the autoimmune disorders among patients. Thus, the further study about female predominance should be needed.

Our study has several limitations. First, it was a retrospective nonrandomized comparative study, and the time of symptomatic onset, which was used to determine whether the patient should be assigned to group I or II, was determined by the patients themselves and not by a clinician. For studies such as the one presented, some biases do exist. In addition, the sample size in our study was relatively small, and this may have influenced the analysis of the relationship between time of onset and pupillo-accommodative dysfunction. Finally, most of the patients failed to complete the follow-up, and were unable to notify us of the duration of their syndrome. However, all the aforementioned findings suggest that there is no relationship between time of onset and dysfunction of pupil reflex in patients with tonic pupil.

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