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A Novel Approach to the Assessment of Afferent Pupillary Defects

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Summary

The pupil response to a flashing light stimulus was observed for a group of 26 healthy volunteer controls, and 15 patients with relative afferent pupillary defects (RAPDs). For the control group, the mean interval between flashes which would just produce a perceptible pupil response was 295 milliseconds (ms). The mean difference between right and left eyes was 8.84 ms. The mean difference between normal and abnormal eyes of the APD group was 78.6 ms. The difference between these results and those of the control group are highly significant statistically ($p<0.001$), and we conclude that this test may be of use in the assessment of defects of the afferent light pathways.

The relative afferent pupillary defect (RAPD) is an extremely useful clinical sign, giving information in a wide range of conditions which involve the pre-geniculate visual pathways.[1–13] Assessment of a RAPD may aid diagnosis and influence management.

In order to chart the course of a disease, and to enable a comparison between the affected eyes of different patients, it is useful to measure the amount of RAPD present. Some clinicians assign a numerical grade to the RAPD. Such rough rating systems are highly subjective and prone to error.[14] The measurement of RAPDs using neutral density (ND) filters has been strongly advocated by some authors.[14,15,16] However, there are technical problems associated with this method. The quantification of RAPDs with ND filters is influenced by the test light used,[17] and causes asymmetric bleaching of the retinas.[14] The 'blanket' reduction in afferent input produced by ND filters is not necessarily the same afferent defect as the one to be matched.

The pupil cycle time has been suggested as a useful clinical test for assessment of optic nerve function.[18,19,20] This test utilises efferent and afferent pathways for the eye under observation. Whereas the RAPD is a relative sign, which disappears if the other eye develops a matching dysfunction, the pupil cycle time is objective for each eye individually and can be used even in monocular patients. However, the pupil cycle time is a difficult and time-consuming test to perform. Moreover, it is a relatively insensitive indicator of optic nerve disease.[3]

It was our aim to produce a test of afferent visual pathway function which was easy and quick to perform, and which would allow the measurement of the RAPD directly. Pupillographic studies of afferent pupillary defects show that when the affected eye is stimulated the pupillary contraction has a longer latent period and a smaller amplitude than when the unaffected eye is stimulated.[9] Since the abnormal response is of greater latency and reduced amplitude, we reasoned that the observed pupillary response to a flashing light would be diminished, and that disappearance of visible response with increasing flash fre-

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Table I. *Age, sex and pupil response measurements in milliseconds of control population*

No.	*Age*	*Sex*	*Right*	*Left*	*Difference*
1	22	F	240	240	0
2	23	F	250	240	10
3	32	M	290	310	20
4	21	F	240	260	20
5	20	F	250	260	10
6	30	M	320	320	0
7	25	M	330	340	10
8	45	F	220	240	20
9	42	M	310	320	10
10	37	F	320	360	40
11	30	M	320	330	10
12	43	F	320	330	10
13	29	F	320	310	10
14	58	F	350	350	0
15	38	F	330	330	0
16	24	F	260	270	10
17	26	M	350	350	0
18	21	F	320	320	0
19	24	F	290	270	20
20	23	F	260	250	10
21	22	F	270	260	10
22	23	F	250	240	10
23	75	M	330	330	0
24	70	M	320	320	0
25	76	F	300	300	0
26	78	M	290	290	0

quency could be used as an end-point for assessment of RAPDs.

Method

Subjects were enrolled for the study from the general ophthalmic outpatient clinic. Assessment of RAPDs was carried out by noting any asymmetry of pupillary escape during the swinging flashlight test, using a bright light in a dim room with the patient fixating a distant target.[1,5,14,21–24] The control population comprised healthy volunteers with no history of ocular disease. For all subjects a full medical, drug and ophthalmic history was obtained. Visual acuity, refractive error, and pupil size were recorded.

Pupil responses were stimulated with flashes of white light from a stroboscope containing a xenon flash-tube, which subjects were asked to view through an eyepiece. The unstimulated eye fixated a distant target in a mirror. Flashes were of 7.5 microseconds duration, and since, at the outset, it was not known if flash intensity would be a significant factor, two intensities were used, namely 42 and 670 cd/s/m^2. The mean background illumination was 15 cd/m^2. The response of the unstimulated eye was observed. The interval between flashes of light was initially 500 milliseconds. This interval was then decreased in 100 millisecond decrements until the pupil response of the unstimulated eye was no longer perceptible. The interval between flashes at which this occurred was recorded and the test was then performed on the other eye. For each eye the test was then repeated starting at the first end-point and increasing the interval between flashes by 10 millisecond increments until a pupil response was just observed. The interval between flashes at which this occurred was recorded as the final end-point. The test was carried out for each intensity of stimulating light, and the observer was masked with respect to any pupillary abnormality of the subject, and to the flash frequency being used at any particular time.

Results

It was found that the results for the two different flash intensities were almost identical, and therefore only one set of results (those using the 670 cd/s/m^2 flash) are presented here.

Twenty-six healthy volunteer subjects (Table I) were recruited for the study. The mean age of this group was 33.8 years (range 20–76) (Table II). For control subjects the mean interval between flashes at which a pupil response was just perceptible was 295 milliseconds (321 for males and 283 for females) (Table III). The mean difference between the end-point for right and left eyes was 8.84 milliseconds (5.5 for males and 10.5 for females) (Table IV). There was no positive correlation

Table II. *Age distribution of controls and patients with afferent pupillary defects. M = male, F = female*

	Controls		*RAPD group*	
Mean age	33.8	[M36.6, F32.3]	75.1	[M74.3, F76.8]
Range	20–76	[M25–68, F20–76]	61–86	[M61–86, F70–82]
n	26	[M9, F17]	15	[M10, F5]

Table III. *Pupil responses, in milliseconds of interval, of control population. SD = standard deviation*

	Mean (SD) for all	*Means (SDs) for sexes*
Right	294 (37.5)	[M317 (19.2), F281 (39.2)]
Left	295 (38.0)	[M323 (17.3), F284 (41.5)]
Both	295 (38.2)	[M321 (18.0), F283 (39.8)]

between the difference in end-point between the two eyes of this group, and the age of the subjects.

Fifteen patients with RAPDS (Table V) were recruited for the study. The mean age of these patients was 75.1 years (range 61–86) (Table II). For this group the mean difference in end-point between the normal and abnormal eyes was 78.6 milliseconds (Table VI). The difference between the results for the control and the RAPD populations is highly significant statistically ($p<0.001$ using a one-sided Mann-Whitney test).

Discussion

Since it indicates an imbalance in the pregeniculate light pathways, the RAPD may provide useful clinical information in a wide range of conditions, including optic neuritis,[1,2] ischaemic or compressive optic neuropathy,[1,3] occlusion of the central retinal artery or vein,[1] asymmetrical glaucomatous damage,[4–8] amblyopia,[9,10,11] contralateral to an optic tract lesion,[12] large macular lesions,[5] retinal detachment,[1,5,13] and extensive organic disease of the retina.[1]

In patients with unilateral optic neuropathy the RAPD is more sensitive than the visual evoked potential (VEP) and the pupil cycle time as an indicator of disease.[3] However, the RAPD is of use only when the disease is unilateral, and bilateral disease may be missed, i.e. it does not replace the VEP in detecting past optic neuritis.

The numerical grading of RAPDs, e.g. from 1+ to 4+, is subject to error, e.g. because of pupil size (small pupils make the RAPD seem less),[14] and because it is highly subjective.

The measurement of RAPDs with neutral density filters has been recommended.[14–16] Using this technique the smallest defect that can be measured with confidence is 0.3 log units.[14] This method is not free from technical problems. Above 1.2 log units, the filter is so dense that it becomes necessary to look around it to see the pupil move.[14] The quantification of RAPDs with ND filters is influenced by the test light used,[17] and causes asymmetric bleaching of the retinas.[14] Also, the ND filters cause a reduction in the incident light across the entire retina, which is not necessarily the same afferent defect as the one to be matched. One disadvantage of the RAPD is that it is a relative sign, and therefore disappears if the other eye develops a matching dysfunction.

In patients who are strongly suspected of having an RAPD but in whom pupillary testing is not possible, brightness comparison testing can be helpful, and in some subgroups it can reliably predict the presence or absence of an RAPD, but it is very subjective.[25]

The pupil cycle time may be used to assess optic nerve function.[18–20] A small beam of light focussed at the pupillary margin induces regular, persistent oscillations of the pupil. One hundred cycles may be timed with a stopwatch to the nearest 0.1 sec, and the average time in milliseconds for a single cycle is then termed the pupil cycle time.[18–20] The pupil cycle time is objective for each eye individually. However, it is a difficult test to perform, and can be time-consuming because of blinking and losses of fixation, and it is a relatively insensitive indicator of optic nerve disease.[3]

Our test demonstrated remarkable consistency between the end-points for the two eyes of the control subjects, and between different subjects (Tables I and III). It should be emphasised that the observer was masked with regard to the flash frequency being used. The end-points for individual eyes show a bimodal distribution, the cause for which is not clear, but seems to be related to sex, insofar as all male controls fall into the less rapid response group, whereas the females are predominantly in the more rapid group (Tables I

Table IV. *Mean difference in pupil response between individuals' eyes, in milliseconds of interval, for controls*

	Mean Difference
Male	5.5
Female	10.5
All	8.84

Table V. *Age, sex, diagnosis and pupil measurements in milliseconds of interval of RAPD group. AMD = age-related macular degeneration; POAG = primary open-angle glaucoma; CRVO = central retinal vein occlusion; CRAO = central retinal artery occlusion; AION = anterior ischaemic optic neuropathy; OA = optic atrophy. Diagnosis in brackets = concurrent condition (* = condition in other eye)*

No.	*Age*	*Sex*	*Diagnosis*	*Affected Eye*	*Unaffected Eye*	*Difference*
1	81	M	AMD	310	280	30
2	78	F	POAG	290	280	10
3	82	F	CRVO	520	420	100
4	86	M	CRVO	480	440	40
5	74	F	CRAO (BRVO)*	580	420	160
6	76	M	CRVO (POAG)	550	380	170
7	79	M	CRVO	420	370	50
8	70	F	AION	440	360	80
9	69	M	AION (POAG)	600	330	270
10	81	M	CRVO	340	300	40
11	80	F	CRVO (POAG)	370	330	40
12	70	M	OA	370	330	40
13	61	M	CRVO	340	300	40
14	67	M	CRVO	360	320	40
15	66	M	CRVO (POAG)	360	290	70

and III). This is consistent with the finding that females tend to have a shorter latency on testing of the visual evoked potential than males. There was no significant difference between the two flash intensities used in this study with regard to eliciting these end-points.

Although the mean age of our control subjects was less than that of the RAPD population, it was evident from our control population that there was no positive correlation between subject age and difference in end-point between the two eyes.

The difference between normal and abnormal eyes of those subjects with RAPDs was highly significant statistically (Table VI). It is possible that the end-point for this test is determined in part by the observer's threshold of observation, just as it is when ND filters are used, but as long as the same observer defines the end-point for the two eyes of a patient this should not matter, as the test is a measure of the difference between the two eyes. Provided the same stimulus is used for both eyes of a patient, the value for the pupil response difference could be compared to the values for other patients. In conclusion, this test appears to be of value in measuring the pupil response directly, giving remarkably consistent and highly significant results with a masked observer. Although it requires much further evaluation, including comparison with established techniques for pupil assessment, it is hoped that this test may be of use in the assessment of defects of the afferent light pathways.

Table VI. *Mean difference in pupil response between 'normal' and 'abnormal' eyes, in milliseconds of interval, for patients with RAPD*

	Mean Difference
Normal	343
Abnormal	422
Difference	78.6

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