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Accuracy of Pupil Assessment for the Detection of Glaucoma:

A Systematic Review and Meta-analysis

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Abstract

Objective—To assess the accuracy of using pupillary light reflex (PLR) in detecting glaucoma.

Clinical Relevance—Glaucoma is a specific disease of the optic nerve and is often more severe in 1 eye. When large enough, this asymmetry in disease severity can cause a relative afferent pupillary defect (RAPD). Better detection of RAPDs may be one way to identify persons with glaucoma.

Methods—We searched Medline and Embase through June 2012 and searched bibliographies for relevant studies for additional references. Two authors independently reviewed all articles and selected studies that assessed PLRs in patients with glaucoma. We analyzed data using mixed-effect bivariate summary receiver operating characteristic meta-analysis models.

Results—A total of 30 studies were included in this review. An RAPD was observed in 9% to 82% of patients with glaucoma. Eleven studies with a total of 7271 participants were included in the analysis, and the pooled estimate corresponded to a sensitivity of 0.63 (95% confidence interval [CI], 0.43–0.80) and a specificity of 0.93 (95% CI, 0.85–0.97). After excluding 2 studies that used the swinging flashlight test, the sensitivity increased to 0.74 (95% CI, 0.59–0.85) with a specificity of 0.85 (95% CI, 0.77–0.90). Study designs and different pupil measurement techniques explained part of the heterogeneity between studies.

Conclusions—Patients with glaucoma frequently have an abnormal PLR and comparing the responses between the 2 eyes can in part distinguish between those with glaucoma and those without the disease. Newer instruments and analytic approaches to assess pupil function may improve the performance of pupil screening.

Glaucoma is characterized by progressive loss of retinal ganglion cells and their optic nerve axons, with resultant structural and functional deficits (optic disc damage and visual field loss). Loss of retinal nerve fibers is often asymmetric between the upper and lower retina, and glaucoma damage is often more severe in 1 eye.^{1–3} This asymmetry can be exploited in diagnostic tools for identifying patients with glaucoma.

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The pupillary light reflex (PLR) is an indicator of the afferent input from the retina and optic nerve. Asymmetry in the PLR between the 2 eyes is referred to as a “relative afferent pupillary defect” (RAPD), and it is often a sign of unilateral or asymmetric impairment of the anterior afferent visual pathways. An RAPD is often clinically detectable in patients with glaucoma.⁴

Various techniques have been described to quantify or measure an RAPD. These include subjective grading based on the amount of initial contraction and subsequent re-dilation of each pupil as a bright light is swung (swinging flashlight test [SFT]) with or without the use of neutral density filters to measure more precisely the pupillary response.⁵ The introduction of pupillography has allowed for even more precise quantification of the pupillary response to illumination.⁶ In an attempt to measure the visual field objectively, some have used pupil perimetry to monitor the pupillary constriction in response to perimetric light stimuli directed at different parts of the retina.^{7,8}

In this study, we reviewed techniques for measuring and quantifying PLR in patients with glaucoma. Furthermore, we assessed the accuracy of using those techniques for glaucoma detection.

Materials and Methods

Data Sources and Search Strategy

We searched Medline (literature from 1951) and Embase (from 1947) to identify potentially relevant articles. Our search included combined controlled vocabulary search terms (MeSH and Emtree) and text words for glaucoma, visual field defect, optic neuropathy, retinal nerve fiber layer thickness (study population) and RAPD, SFT, pupillography, pupillometer, pupil perimetry, and PLR (techniques) (Appendix 1, available at <http://aaojournal.org>). All searches were last updated on June 22, 2012, and were not limited by study design or by language. We reviewed the bibliographies of all selected articles and searched Web of Science for articles that cited the selected articles to identify additional studies.

Study Selection

Two authors (D.S.C. and L.X.) independently screened titles and abstracts for inclusion, retrieved potentially relevant studies, and determined eligibility. Any disagreements were resolved by consensus. Studies eligible for inclusion were diagnostic accuracy studies or studies that assessed pupil response in populations including more than 10 patients with glaucoma. Articles without original data or without English abstracts were excluded from this review.

Data Extraction

Extracted data included study design, patient characteristics, study methodology, techniques in measuring pupil responses, definition of RAPDs, and main results (Appendix 2, available at <http://aaojournal.org>). The primary outcome of this review was to assess the accuracy of detecting glaucoma using RAPD. Secondary outcomes included comparing the magnitude of RAPDs in subjects with and without glaucoma and assessing the association between visual field loss and the magnitude of RAPD. Methodological quality for included studies was assessed by one author using the modified QUADAS tool that included 14 mandatory items.⁹

Clinical and Laboratory Techniques

Swinging Flashlight Test—The SFT is a technique for comparing the pupil response to light between 2 eyes; unilateral or asymmetric optic nerve disease is associated with

constriction of both pupils when the flashlight is shone in the better eye but dilation of both pupils when the flashlight is moved to the worse eye. The degree of RAPD can be quantified by placing neutral density filters of increasing light absorption in front of the better eye until the RAPD is neutralized.⁵

Pupil Cycle Time—The observation of pupil cycle time (PCT) was first introduced by Stern¹⁰ in 1944 and further improved by Miller and Thompson¹¹ in 1978. They used a slit-lamp 0.5-mm-thick horizontal beam of light to stimulate a pupil response. The beam is raised from just below the pupil until it overlaps the inferior margin of the pupil, resulting in pupillary constriction. The beam is held in this position so that the constricted iris blocks the light. The pupil then re-dilates until it overlaps the edge of the light beam again, producing another pupil constriction. This results in a persistent oscillation. The PCT is calculated by timing 30 oscillations; the average of 5 measurements of PCT is used.

Pupillography—Infrared video pupillography (IVP) was first introduced in 1958 by Lowenstein and Loewenfeld.⁶ The iris is illuminated by an infrared source, and the reflected light is imaged by a video camera, allowing movements of the pupil to be recorded in darkness. When comparing the 2 eyes, an RAPD can be quantified by alternating the infrared stimulus between the 2 eyes and adjusting the stimulus intensity until the response amplitude is the same or by measuring the difference in response amplitude between the 2 eyes using the same stimulus intensity.

Pupil Perimetry—Most of these tests use full-field stimulation to elicit the pupillary response, that is, the light stimulus illuminates most or all of the fundus and the observed response is the sum of the pupillomotor drive from all areas of the retina. Pupil perimetry, instead, is a pupillometer used to monitor pupil response to light that illuminates only a small region of the visual field. If the defects present in the visual field are generally matched by corresponding defects in the pupil field, pupil perimetry may have potential as an objective and quantitative means of assessing function in different areas of the visual field.^{7,8}

Statistical Analysis

Extracted data were used to create forest plots of sensitivity and specificity to depict study-specific estimates of sensitivity and specificity in receiver operating characteristic space. We applied the mixed-effect bivariate summary receiver operating curve models to derive inferences about diagnostic test accuracy using STATA/SE 12.0 (StataCorp LP, College Station, TX).^{12–14} The bivariate models account for the correlation between sensitivity and specificity observed across studies, which captures the functional relationship between sensitivity and specificity because the threshold varies within each study.

We also investigated whether diagnostic accuracy varied across studies with different pupil assessment techniques. In particular, we performed a prespecified sensitivity analysis to see whether performance improved after excluding studies that used the SFT because this approach is the least sophisticated of the ones studied.

Results

Search Results and Study Characteristics

The electronic database searches identified 1258 citations. We deleted duplicates and assessed the bibliographies of included studies and articles that cited the included studies. A total of 31 articles from 30 studies met inclusion criteria (Fig 1).^{4,15–44} Studies were conducted in more than 11 countries and published in different languages. We did not

translate non-English articles, and 2 articles without an English abstract were excluded from this review. Two studies were population-based studies, 20 studies were case-control, and 8 studies were case series of patients with glaucoma (Tables 1 and 2; Table 2, available at <http://aojournal.org>).

Ten studies assessed the performance of the SFT in glaucoma.^{15–24} In 3 clinic-based studies, an RAPD was documented in 23% to 34% of patients with glaucoma in whom SFT was performed,^{22–24} but the rate was lower in a population-based survey in southern India (9%) and higher in another survey of hospital workers in Nigeria (46%).^{15,16} Other studies of the SFT reported that patients with an RAPD had greater intereye asymmetry of optic nerve damage, visual field loss, or nerve fiber layer thickness compared with those without an RAPD.^{19–21} Lankaranian et al¹⁸ assessed subjective RAPD in 70 patients with glaucoma using the standard SFT and a magnifier-assisted SFT, and both methods showed good agreement regarding the presence of an RAPD compared with pupillography (63% and 79% agreement). Others compared magnifier-assisted and ophthalmoscopy-assisted SFT with the standard method and reported that the magnifier-assisted method was the most sensitive for detecting an RAPD at any level of intereye difference in mean deviation or disc damage likelihood score. However, specificities were not reported in this study.¹⁷

Although no studies have been published in the past 15 years assessing PCT, one group found that PCT measurements are prolonged in eyes with open-angle glaucoma (1231 vs. 942 ms in age-similar controls; $P < 0.001$).²⁵ Another study measured PCT in 118 patients with angle-closure glaucoma (ACG) and 70 age- and sex-matched control subjects.²⁶ Pupillary oscillation in response to edge-light stimulation was absent in 46% of the patients with ACG but in only 10% of controls. Among those who had pupillary oscillation, PCT was longer in patients with ACG than in controls (1070 vs. 968 ms).

Twelve studies assessed pupil response using pupillography.^{4,27–38} Studies generally have reported a higher detection rate of RAPD in patients with glaucoma using IVP (29%–68% overall, and 82% for asymmetric glaucoma) compared with studies using the SFT (9%–46%).^{31,33–37} The findings of these studies are as follows: (1) RAPD is more likely to be present in patients with glaucoma than in controls.^{33–35} (2) Patients with glaucoma have greater asymmetry in the IVP between the 2 eyes (as measured by pupil area ratio)^{4,32} and greater differences in response to light between the superior and inferior visual field within the same eye.^{29,30} (3) Eyes with glaucoma have smaller amplitude, slower velocity, and slower acceleration of pupil constriction than control eyes.^{32,34,38} (4) Glaucomatous eyes have smaller sustained constriction of PLR after cessation of blue light stimuli compared with controls.^{27,28}

Six studies reported the performance of pupil perimetry in patients with glaucoma.^{39–44} Aoyama⁴⁴ included patients with visual field defects from a variety of diseases, and the article was written in Japanese; thus, limited information was available to extract. Three other studies from a single group stimulated 24 or 40 retinal regions arranged in a dartboard pattern.^{39–41} They found that response amplitudes were smaller and times to peak constriction were delayed in patients with glaucoma compared with controls. Two other studies conducted in Japan linked the pupillometer to an automated perimeter using a Goldmann size V stimulus in 76 locations.^{42,43} The visual field obtained by pupil perimetry was expressed by mapping the amount of the pupil constriction in a gray scale at each target location within the field. In general, defects present in the visual field were matched by corresponding defects in the pupil field, but no quantitative comparisons were presented.

Quality Assessment

A total of 28 of 30 studies included only a series of patients with glaucoma or some subjects without glaucoma as controls (Fig 2). Approximately 70% of the included studies had clearly defined eligibility criteria, glaucoma diagnosis, and reasons for patient exclusion. Because most studies were cross-sectional, the index test (pupil assessment) and reference standard (visual field, nerve fiber thickness, or optic nerve assessment) were often collected within a short period of time. A delay of a few days to a few months is unlikely to result in disease progression bias. The definition of glaucoma varied across studies, and some studies did not state clearly how glaucoma was defined. But it is unlikely any patients received different reference standard tests based on the condition of their pupil response. Most studies described in sufficient detail how the pupil assessment and the reference standards were executed, but few studies masked the persons who performed the tests from the diagnosis. This is less important for automated testing or testing where a digital output is provided by a machine, but nevertheless does allow for inappropriate data manipulation to occur. Incorporation bias, which occurs when the test being evaluated is incorporated in a composite reference standard, often leading to overestimation of diagnostic test accuracy, was not present in any study. Only 3 studies reported any uninterpretable results or missing data. Failure to report this may lead to a biased assessment of the test performance. Because all included studies were cross-sectional and none reported on withdrawals, we were not able to assess the last item of QUADAS (*were withdrawals from the study explained?*).

Evidence Synthesis

Among the 30 studies, 10 did not include normal subjects as a control group and 9 did not report the accuracy of glaucoma detection. This left 11 studies with a total of 7271 participants to be included in the analysis (Fig 3). The receiver operating characteristic scatter plot shows greater variability in estimated sensitivity than specificity across studies (Fig 4A). The 2 studies with low sensitivity (9%–28%) were population-based, and they used SFT with only limited standardization.^{15,16} Nine other clinic-based, case-control studies used pupillography to measure pupil constriction.^{4,28–30,33–35,39,41} The differences in study design and study techniques explain part of the heterogeneity across studies. The meta-analytic summary estimates of the 11 studies corresponded to a sensitivity of 0.63 (95% confidence interval [CI], 0.43–0.80) and a specificity of 0.93 (95% CI, 0.85–0.97). The positive likelihood ratio was 8.9 (95% CI, 5.1–15.8), the negative likelihood ratio was 0.4 (95% CI, 0.2–0.6), and the diagnostic odds ratio was 22.7 (95% CI, 14.0–36.9). We also conducted a separate analysis excluding the 2 studies using SFT, and the sensitivity increased to 0.74 (95% CI, 0.59–0.85) with a specificity of 0.85 (95% CI, 0.77–0.90) (Fig 4B).

Discussion

This review of the literature shows that an RAPD is present in patients with glaucoma, but estimates range widely in the literature. The severity of an RAPD correlates with the amount of visual field loss and the extent of optic nerve damage. Furthermore, assessing pupil function to detect glaucoma seems highly specific (>90%). On the basis of a meta-analysis of the reported data, pupillography has a sensitivity of approximately 75% with a specificity of 85% in clinic-based studies.

The SFT is the most commonly performed test of pupil function in clinical practice. It is quick and quantifiable using neutral density filters. However, the test requires considerable practice to perform reliably, as well as care in its interpretation. An RAPD as small as 0.3 log units can be detected clinically, but the presence of an RAPD implies that significant retinal ganglion cell injury has occurred. In rhesus monkeys, an RAPD measuring 0.6 log

units develops after an approximate unilateral loss of 25% to 50% of retinal ganglion cells.⁴⁵ The introduction of high-resolution IVP has improved our ability to detect even subtle RAPDs. When compared with SFT, pupillography was found to be more sensitive in detecting mild abnormalities, and the identification of an RAPD in persons with glaucoma was generally higher. However, IVP can be abnormal in persons without glaucoma, which may reduce the specificity of the test.

Because tests for an RAPD compare the pupil response between eyes, they cannot detect bilateral or symmetric disease, nor can the results be easily compared between patients. Another clinical test that does not require a normal fellow eye for comparison is the measurement of PCT. However, the test takes approximately 5 minutes, which is a long time for both the patient and the observer to concentrate at the slit-lamp. The background conditions and intensity of the stimulus have not been standardized. Although some studies have reported prolonged PCT in eyes with glaucoma, the difficulty of performing this test has resulted in no studies using this approach being published in the past 15 years.^{25,26}

In normal eyes, the distribution of nerve fiber bundles is relatively symmetric about the horizontal meridian, whereas early glaucoma damage is often greater in the superior or inferior retina. On the basis of this knowledge, Wride et al²⁹ and Chen et al³⁰ compared the relative difference of PLR in the upper and lower hemifields and found 70% to 85% agreement with clinical diagnosis. Attempts to measure pupil response to patterned light stimuli have been made to assess ganglion cell function in different areas of the visual field. Results from small studies have found that defects present in the visual field are generally matched by corresponding defects in the pupil field.^{42,43} The spatial resolution in pupil perimetry is poorer than in visual field perimetry because larger stimuli are needed to elicit reliable pupil responses. Further studies are needed to determine whether this approach could be used to screen populations for glaucoma.

Because of progressive loss of retinal ganglion cells and their optic nerve axons, it is likely that the pupil response in eyes with glaucoma will be diminished when compared with normal eyes. Studies have confirmed that patients with glaucoma have lower amplitude, slower velocity, and acceleration of pupil constriction than control subjects.^{30,32,34} Determining the exact onset and peak contraction of the pupil is a major challenge when trying to determine whether single eye pupillary responses are abnormal. The action of the smooth iris sphincter muscle does not always cause an abrupt change in the pupil tracing. Despite previous studies of pupil assessment, there is still no agreement on the optimal method for this measurement, and there is not much information on the variability of PLRs between eyes and among normal subjects.⁴⁶ In addition, factors unrelated to optic nerve damage, such as mechanical properties of the iris, and other systemic conditions or use of medications also may contribute to the variability of PLRs.

Given that the majority of the studies included clinic patients with known or suspected diseases, the evidence is not applicable to routine screening and primary care settings, and the estimates of sensitivity and specificity may be overestimates of the true effect.^{47,48} Testing procedures for pupil assessment were not standardized, and there is no consistent cutoff for each measurement. Therefore, it is difficult to combine or compare results of different studies, and we were able to pool results from only 11 of 30 included studies. By removing SFT testing, it seems that some of the heterogeneity seen is explained by the limitations of that test. Other factors, such as different protocols used in each study, different characteristics of study participants, and different types and severity of glaucoma damage, also may contribute to some heterogeneity across studies. However, we were not able to conduct subgroup analyses because there were a limited number of studies and patient-level or subgroup data were not reported. We identified variability in the reference standard, with

some investigators relying on clinical examination only, some defining standards that incorporated clinical examination with both structural and functional measurements, and some not reporting this in the article. The lack of an agreed on reference standard for the diagnosis of glaucoma and a standard study protocol were additional limitations of this review. A final limitation was our exclusion of non-English language publications because some studies were identified that were published in other languages, and we could extract only limited information from the abstracts.

In this review, we did not identify any study directly comparing pupil assessment with other diagnostic tests. On the basis of previous systematic reviews, the pooled estimate of the sensitivity of the tests in detecting glaucoma ranged from 46% (Goldmann applanation tonometry) to 92% (frequency doubling technology perimetry C-20-1), whereas specificity ranged from 75% (frequency doubling technology perimetry C-20-5) to 95% (Goldmann applanation tonometry).^{49,50} The pooled sensitivity and specificity of pupillography is similar to those estimates. However, high heterogeneity was found across studies for most tests, and it is not possible to conclude which test (or a group of tests) is the most accurate.

In conclusion, the available evidence suggests that patients with glaucoma often have an abnormal pupil response to illumination. The measurement of pupil response to light provides an objective test of visual function, which identifies a substantial portion of those with glaucoma in some studies. However, there is insufficient evidence from population-based research assessing pupil response under controlled conditions to support wider use of this approach. Also, an RAPD is relatively nonspecific and may be caused by a number of conditions other than glaucoma. Future studies investigating conditions and confounders affecting pupil responses and methods improving the accuracy of glaucoma detection would be useful.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Flow of study selection.

	Hennessy 2011 ¹⁵	Agbeja 2003 ¹⁶	Ichhpujani 2010 ¹⁷	Lankaranian 2005 ¹⁸	Chew 2010 ¹⁹	Brown 1987 ²⁰	Tatsumi 2007 ²¹	Schiefer 2012 ²²	Skorkovska 2011 ²³	Page 1985 ²⁴	Bojic 1993 ²⁵	Clark 1986 ²⁶	Feigl 2011 ²⁷	Kankipati 2011 ²⁸	Wride 2009 ²⁹	Chen 2008 ³⁰	Kalaboukhova 2007 ³¹	Kalaboukhova 2006 ³¹	Link 2006 ³²	Jonas 1990 ³³	Ichihashi 1993 ³⁴	Hashimoto 1991 ³⁵	Hashimoto 1990 ³⁶⁻³⁷	Brazier 1989 ³⁸	Carle 2011 ³⁹	James 2011 ⁴⁰	Maddess 2009 ⁴¹	Asakawa 2010 ⁴²	Yoshitomi 1999 ⁴³	Aoyama 1977 ⁴⁴
1. Representative spectrum?	+	+	?	?	-	-	-	-	-	-	?	-	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	-
2. Clear selection criteria?	+	+	+	+	+	+	+	?	?	?	?	+	+	+	+	+	+	+	+	-	?	?	?	?	+	+	+	+	+	?
3. Acceptable reference standard?	+	+	+	+	+	+	+	+	+	+	?	+	+	+	+	+	+	+	+	?	?	?	?	+	?	+	+	+	+	+
4. Acceptable delay between tests?	+	+	+	+	+	+	+	?	?	?	?	+	?	?	+	+	+	+	+	?	?	?	?	?	+	?	+	+	+	?
5. Partial verification avoided?	-	+	+	+	+	+	+	+	+	+	?	+	+	+	+	-	+	+	+	?	?	?	?	?	?	+	+	+	+	?
6. Differential verification avoided?	-	+	+	+	+	+	+	+	+	+	?	+	+	+	+	+	+	+	+	?	?	?	?	+	+	+	+	+	+	?
7. Incorporation avoided?	+	+	+	+	+	+	+	+	?	+	+	+	+	+	+	+	+	+	+	+	?	?	?	+	+	+	+	+	+	+
8. Detailed index text?	-	-	+	+	+	+	+	-	?	+	+	+	+	+	+	+	+	+	+	+	?	?	?	+	+	+	+	+	+	?
9. Detailed reference standard?	?	?	+	+	+	+	+	+	?	?	-	+	+	+	?	+	+	+	+	-	?	?	-	-	+	+	+	+	+	?
10. Reference standard results blinded?	-	-	+	+	-	-	-	-	?	-	-	-	-	-	-	-	-	-	-	+	?	?	-	-	-	-	-	-	-	?
11. Index test results blinded?	+	-	+	+	+	-	+	?	-	?	-	-	-	-	-	-	-	-	+	+	?	?	-	-	-	-	-	-	-	?
12. Relevant clinical information?	-	-	-	?	?	?	?	-	-	-	?	?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
13. Uninterpretable results reported?	-	-	-	-	-	-	-	?	-	-	-	-	-	-	+	-	+	-	-	-	?	?	-	-	-	+	+	-	-	?
14. Withdrawals explained?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?

-	No
?	Unclear
+	Yes

QUADAS tool

1. Was the spectrum of patients representative of the patients who will receive the test in practice? (Yes, if population based study; Unclear, if studies included both glaucoma patients and controls; No, if studies only included glaucoma patients).
2. Were selection criteria clearly described?
3. Is the reference standard likely to correctly classify the target condition?
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?
6. Did patients receive the same reference standard regardless of the index test result?
7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard?)
8. Was the execution of the index test described in sufficient detail to permit replication of the test?
9. Was the execution of the reference standard described in sufficient detail to permit its replication?
10. Were the index test results interpreted without knowledge of the results of the reference standard?
11. Were the reference standard results interpreted without knowledge of the results of the index test?
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
13. Were un-interpretable/intermediate test results reported?
14. Were withdrawals from the study explained?

Figure 2.
Methodological quality summary for each included study.

Figure 3.

Forest plot of included studies. The estimated sensitivity and specificity of the study (*square*) and its 95% CI (*horizontal line*) are shown. The *diamonds* represent the summary estimates of all 11 studies (COMBINED N=11, A+C+D) or the sensitivity analysis of 9 studies, excluding 2 that used SFT (COMBINED N=9, C+D). Swinging flashlight test (A), pupillography (C), and pupil perimetry (D). Numbers in parentheses indicate the corresponding reference.

Figure 4.

A, The summary receiver operating curve (SROC) plot for detection of glaucoma. The *solid line* is the summary receiver operating characteristic curve along with its 95% prediction region, which gives an indication of between study heterogeneity. The *solid square* represents the summary sensitivity and specificity points along its 95% confidence intervals. Swinging flashlight test (SFT) (**A**), pupillography (C), and pupil perimetry (D). Numbers in brackets indicate the corresponding reference. **B**, The summary receiver operating curve plot of the sensitivity analysis, excluding 2 studies that used the SFT in pupil assessment. C, Pupillography. D, Pupil perimetry. Numbers in brackets indicate the corresponding reference.

Table 1

Study Design and Results of Studies Included in the Meta-Analysis

Source	Study Design	Measure and Definition of RAPD	Outcome Results
Hennessy et al, ¹⁵ 2011 India	Population-based, cross-sectional (Aravind Comprehensive Eye Survey) Glaucoma (n=77) No glaucoma (n=4992)	SFT, not standardized Household/village test and comprehensive (hospital-based) testing for RAPD	Sensitivity: 9.1% (7/77) Specificity: 99.3% (4956/4992)
Agbeja-Baiyerolu et al, ¹⁶ 2003 Nigeria	Population-based, cross-sectional (hospital workers) Glaucoma (n=57) Suspects (n=315) Normal (n=1,737)	SFT, unclear method of testing for and definition of RAPD	RAPD: 0.5% for right eye and 1.1% for left eye 46% of RAPDs were definite glaucoma (5/11 for right eye, 11/24 for left eye)
Wride et al, ²⁹ 2009 UK	Case-control study Glaucoma (n=30) Normal (n=30)	Pupillometry (Pupilmatrix PLR60), * monocular, with 3 stimulus pairs: paracentral, Bjerrum, and peripheral of mirror images about the horizontal meridian No RAPD	AUROC = 0.907±0.041 (SE) (95% CI, 0.802–0.967) Sensitivity: 93.1% (95% CI, 77.2–99.2) Specificity: 76.7% (95% CI, 57.7–90.1)
Chen et al, ³⁰ 2008 USA	Case-control study Glaucoma (n=40) Normal (age similar, n=40)	Infrared pupillometry, monocular, with paracentral, Bjerrum, and peripheral of mirror images about the horizontal meridian Relative pupillomotor sensitivity: corresponding superior and inferior retinal territories within the same eye No RAPD	Contrast balance (relative sensitivity to the upper and lower stimuli): AUROC = 0.83 Combined contrast balance and pupil amplitude: AUROC = 0.88
Kalaboukhova et al, ⁴ 2007 Sweden	Case-control study POAG (n=30) Normal (n=30)	Pupillometer, binocular, with full field stimulation PAR PCVR PDVR	PAR: 1.4 vs. 1.1 (glaucoma vs. control), AUROC = 0.92, sensitivity 90%, specificity 87% PCVR: 1.1 vs. 1.07 (glaucoma vs. control) AUROC = 0.61 PDVR: 1.2 vs. 1.08 (glaucoma vs. control) AUROC = 0.76
Kalaboukhova et al, ³¹ 2006 Sweden	Case-control study Glaucoma (n=17 asymmetric) Normal (n=15)	Infrared pupillometry, binocular, with alternating full-field stimulus	PAR: AUROC = 0.93, sensitivity 82.4%, specificity 86.7% Intereye difference in visual field correlated with PAR deviations
Jonas et al, ³³ 1990 Germany	Case-control study POAG (n=17) Normal (n=10)	Pupillometry, monocular RAPD: the difference in pupillary diameter between the 2 eyes at the same background illumination 0.5 mm	RAPD in 0/10 normal eyes and in 35% (7/17) POAG eyes RAPD correlates with the intereye difference in neuroretinal rim area, CDR, and RNFL (no numeric data available)
Ichihashi et al, ³⁴ 1993 (English abstract) Japan	Case-control study Glaucoma (n=14) Suspects (n=9)	Pupillography, monocular, with colored stimuli No RAPD	4/14 glaucoma eyes with and 1/9 glaucoma suspect eyes showed decreased constriction rates (%) to stimuli of all wavelengths
Hashimoto et al, ³⁵ 1991 (English abstract) Japan	Case-control study POAG (n=11) OH (n=11)	Infrared videopupulogram Unclear RAPD definition	RAPD in 1/22 OH eyes and 15/22 POAG eyes
Carle et al, ³⁹ 2011 Australia	Case-control study POAG (n=17) Normal (n=19)	Multifocal pupillographic perimetry (40 region stimulus, circular dart-board-like), binocular Less sparse steady (0 Hz, duration 33 msec, interval 1 sec) Less sparse flicker (20 Hz, duration 100 ms, interval 1 sec) Moderate sparse flicker (20 Hz, duration 100 msec, interval 4 sec) High sparse flicker (20 Hz, duration 150 msec, interval 16 sec)	High sparse flicker protocol: AUROC = 0.86 Smaller mean response amplitudes, delayed time to peak values, shorter time courses, and smaller pupillary constriction widths in patients with glaucoma compared with normal across all protocols
Maddess et al, ⁴¹ 2009 Australia	Case-control study Glaucoma (n=26) Normal (age, sex matched) (n=20)	Multifocal pupillographic perimetry (24 region stimulus, circular dart-board-like), binocular Single large patch, steady (On1)	AUROC = 0.84 for On1 Smaller constriction amplitudes, delayed time to peak values in patients with glaucoma compared with normal

Source	Study Design	Measure and Definition of RAPD	Outcome Results
		Single large patch, flicker (F11) 4 quadrangular patches, steady (On4) 4 quadrangular patches, flicker (F14)	

AUROC = area under the receiver operating characteristics curve; CI = confidence interval; CDR = cup-to-disc ratio; OH = ocular hypertension; PAR = pupil area ratio; PCVR = pupil contraction velocity ratio; PDVR = pupil dilation velocity ratio; POAG = primary open-angle glaucoma; RAPD = relative afferent pupillary defect; RNFL = retinal nerve fiber layer; SE = standard error; SFT = swinging flashlight test.

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