An Algorithm for Glaucoma Screening in Clinical Settings and Its Preliminary Performance Profile

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Purpose: To devise and evaluate a screening algorithm for glaucoma in clinical settings.
Methods: Screening included examination of the optic disc for vertical cupping (≥0.4) and asymmetry (≥0.15), Goldmann applanation tonometry (≥21 mmHg, adjusted or unadjusted for central corneal thickness), and automated perimetry. In the diagnostic step, retinal nerve fiber layer imaging was performed using scanning laser polarimetry. Performance of the screening protocol was assessed in an eye hospital-based program in which 124 non-physician personnel aged 40 years or above were examined. A single ophthalmologist carried out the examinations and in equivocal cases, a glaucoma subspecialist’s opinion was sought.
Results: Glaucoma was diagnosed in six cases (prevalence 4.8%; 95% confidence interval, 0.01-0.09) of whom five were new. The likelihood of making a definite diagnosis of glaucoma for those who were screened positively was 8.5 times higher than the estimated baseline risk for the reference population; the positive predictive value of the screening protocol was 30%. Screening excluded 80% of the initial population.
Conclusion: Application of a formal screening protocol (such as our algorithm or its equivalent) in clinical settings can be helpful in detecting new cases of glaucoma. Preliminary performance assessment of the algorithm showed its applicability and effectiveness in detecting glaucoma among subjects without any visual complaint.

Keywords: Glaucoma Screening; Clinical Setting Screening; Chronic Glaucoma; Screening Algorithm; Screening Test Performance

INTRODUCTION

Glaucoma is the second cause of preventable blindness in the world.1,2 The prevalence of open angle glaucoma is estimated at 2-7% in people aged over 40 years.3-5 In 2002, the World Health Organization (WHO) estimated that out of 36 million blind people, more than 12% is due to glaucoma.6 Unfortunately, it is predicted that the number of glaucoma blindness will increase
to 11.1 million by 2020. Even in developed countries, up to 50% of glaucoma cases are not diagnosed in a timely manner, while 90% of patients in developing countries do not receive proper care. WHO has reported glaucoma and diabetic retinopathy as new emerging causes of blindness in Iran.

Glaucoma is considered as an ideal condition for screening programs as it fulfills almost all of the required criteria; the disease has a long preclinical phase with insidious onset, symptomless progression, and diverse therapeutic modalities. Nowadays, with the advent of computer assisted imaging systems, we can (with higher level of certainty) tell if a subject is affected by glaucoma or not, even in subclinical stages.

Three population frameworks are described for glaucoma screening: the community at large, high-risk populations, and clinical populations. Most studies failed to show convincing efficiency for community-based glaucoma screening programs for several reasons: inefficiency in targeting the high-risk population, high false positive rates, suboptimal accuracy of screening tests (high rate of false negative), impracticality of some techniques, incomplete uptake of screening, limited access to further diagnostic investigations, unwarranted follow-up, and matters of cost. In fact, successful detection has not consistently led to a fruitful outcome as follow-up and care of a glaucoma case needs commitment by both the patient and the ophthalmologist.

Screening for glaucoma in clinical settings (i.e. eye care centers) is the least controversial. There is ample opportunity for glaucoma screening in middle-aged ophthalmic referrals: the prevalence of glaucoma is relatively higher, more accurate diagnostic investigations are available, and such patients have an established connection with the clinical facility. It is believed that this opportunity for screening remains underutilized.

In this study, we intended to develop an objective algorithm for glaucoma screening in clinical settings for patients with no specific complaint of visual loss. Performance of the algorithm was appraised in a healthy adult population.

**METHODS**

**Screening Algorithm**

Based on literature review and expert consultation, the following examinations and investigations were selected:

**Tonometry**

Single Goldmann appplanation tonometry readings with and without adjustment for central corneal thickness were recorded. Any intraocular pressure (IOP) greater than or equal to 21 mmHg was considered as ocular hypertension (OHT). Central corneal thickness was measured using Pentacam HR (Oculus, Wetzlar, Germany) and Ehlers correction was applied to refine tonometry readings.

**Funduscopy**

The optic discs were evaluated clinically in terms of vertical cup-to-disc ratio (VCDR) and inter-eye asymmetry, using a +90 diopter fundus lens by a single ophthalmologist (SFM). VCDR of ≥0.4 and asymmetry ≥0.15 were considered as abnormal optic disc features. Fundus examination was performed through a dilated pupil unless there was a contraindication for mydriasis.

**Visual Fields**

Humphrey automated threshold perimetry (Humphrey Field Analyzer, model 750, Carl Zeiss Meditec, Dublin, CA, USA) using the Swedish Interactive Threshold Algorithm (SITA) standard central 24-2 protocol was performed for subjects with abnormal optic discs. The test was repeated until a reliable result was achieved. To identify possible abnormalities, we used the Glaucoma Hemifield Test (GHT) result and Pattern Standard Deviation (PSD). A GHT result of “outside normal limits” and/or PSD probability level of <1% were suggestive of glaucoma. Borderline GHT results were also documented. Visual field (VF) tests were reviewed for reliability to exclude unreliable ones. Internal reliability thresholds for the
Humphrey SITA Standard central 24-2 protocol included 5% for false positive and 7% for false negative rates (Figure 1).

**Diagnosis**

In the diagnostic step, retinal nerve fiber layer analysis was performed using scanning laser polarimetry (GDx VCC, software 5.5.0.14, Carl Zeiss Meditec, Inc., Dublin, CA, USA). This test was performed in subjects who had borderline VFs or OHT without abnormal appearing optic discs. The test was considered abnormal when there was a typical wedge shaped defect consisting of super-pixels of P<0.01 extending to the optic nerve margin. Further investigations included repeated and diurnal IOP measurements and gonioscopy. Diagnostic evaluations were carried out in collaboration with a glaucoma subspecialist (SM). A single ophthalmologist performed screening and complementary evaluations throughout the study (SFM).

**Figure 1.** Screening and diagnostic algorithm for glaucoma; the algorithm consisted of serial and simultaneous combinations of tests. The authors did their best to objectify their approach but not all the clinical acumen can be incorporated in the form of an algorithm and clinicians should employ their intuition in practice. Note that there were 26 abnormal screening findings in 20 subjects. Gonioscopy was performed in the Diagnosis stage.

CCT, central corneal thickness; IOP, intraocular pressure; cIOP, CCT-adjusted IOP; VCDR, vertical cup disc ratio; CDR, cup-disc ratio; SITA, Swedish Interactive Threshold Algorithm; OHT, ocular hypertension; NTG, normal tension glaucoma.
Subjects

The performance of the algorithm was assessed on 124 non-physician staff of Farabi Eye Hospital aged ≥40 years in 20 sessions. Demographic characteristics, history of previous IOP measurement, and family history of glaucoma in first-degree relatives were ascertained. Subjects with a history of cataract surgery, significant ocular trauma and stroke were examined but excluded from the study population. The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences Research Council and conformed to the tenets of the Declaration of Helsinki.

Performance Assessment

Positive predictive value (PPV) represents the proportion of test-positive subjects who truly have the disease. It was measured by dividing the number of cases who were diagnosed as glaucomatous (true positive) by the total number of individuals who had abnormal findings in the screening (true positive plus false positive). The proportion of post- and pre-test odds of having glaucoma (pre-test odds of a condition is the prevalence of that condition in a population) measures the positive likelihood ratio of the screening algorithm.

RESULTS

One hundred and twenty-four individuals with mean age of 46±4.5 years including 72 (58.1%) female subjects were screened. The screening result was positive in 20 (16.1%) subjects who underwent further diagnostic evaluations (Figure 1). Finally, glaucoma was diagnosed in 6 (4.8%) participants, including 3 cases of open-angle glaucoma, one patient with arrested glaucoma/normal tension glaucoma, and two individuals with early glaucoma. OHT was diagnosed in two other subjects. Two eyes had a history of keratorefractive surgery for which suitable IOP adjustment was made. The eyes were otherwise normal except for occasional mild to moderate dry eye, presbyopia and refractive errors.

About one quarter of screened subjects had history of prior IOP measurement and 15 individuals (12.1%) reported a positive family history of glaucoma. Only one subject had previously been diagnosed with glaucoma.

The odds of having glaucoma before performing the examination (based on the observed frequency of glaucoma in Iran) was at least 6/118 while the post-screening odds was 6/14; this translates into a positive likelihood ratio of 8.4. The PPV of the screening protocol was 30%.

| Variable | Frequency (%) |
|----------|---------------|
| Baseline characteristics | |
| Female | 72 (58.1) |
| Age (year ± standard deviation) | 46.0 ± 4.5 |
| Smoking | 17 (13.7) |
| Having a university degree | 49 (39.5) |
| Nursing profession | 39 (31.5) |
| History of prior IOP measurement | 30 (24.2) |
| A positive family history of glaucoma | 15 (12.1) |
| Ocular findings | |
| Right | Left |
| IOP (mmHg) | 16.1 | 16.2 |
| Corrected IOP (mmHg) | 17.1 | 16.9 |
| CCT (microns) | 529.4 ± 40.4 | 531.2 ± 41.6 |
| VCDR | 0.26 | 0.26 |
| AC depth (from endothelium, mm) | 2.8 | 2.8 |
| Spherical equivalent RE (diopter) | |
| Mean absolute | 1.11 ± 1.1 | 1.11 ± 1.1 |
| Range | -7.0 to +5.1 | -6.1 to +7.2 |
| Asymmetric optic disc, n (%) | 6 (4.8) |

IOP, intraocular pressure; CCT, central corneal thickness; VCDR, vertical cup-disc ratio; AC, anterior chamber; RE, refractive error
Corneal thickness adjustment increased the total number of abnormal IOPs into 28 eyes versus 14 eyes without adjustment and increased mean IOP from 16.2 mmHg in unadjusted measures to 17 mmHg (paired sample t-test; \(P=0.004\)). On fundus examination, 12 subjects (21 eyes) had abnormal VCDR and/or VCDR asymmetry according to our criteria.

**DISCUSSION**

In clinical settings, at least at our center, ophthalmologists are after glaucoma in quite broad ways, from digital estimation of IOP to applanation tonometry; and to inspection and comparison of the optic discs. It has been reported that half of the patients with a recent diagnosis of glaucoma had an eye examination in the preceding 12 months but still had been missed.27 Good practice does not support the opportunistic case-finding approach for glaucoma.28

In this study, we developed and tested an algorithm for glaucoma screening in a clinical setting. Our screening protocol sorted out 80% of the population pool as normal, while the other 20% with abnormal findings had an 8.4 times higher likelihood of having glaucoma. In other words, a positive result of this screening protocol adds at least 40% to the pre-test probability of having glaucoma. The PPV of the screening algorithm was 30%. These performance indices are comparable to optimal screening strategy indices introduced by Robin et al;29 they suggested combining visual acuity and family history with frequency doubling technology (FDT) and Heidelberg Retinal Tomography (HRT) for population based screening of glaucoma.

In the current study, subjects with normal ocular findings were not evaluated any further, i.e. visual fields and/or retinal nerve fiber layer imaging. Therefore, performance indices such as sensitivity, specificity, negative predictive value, negative likelihood ratio and accuracy cannot be established for our algorithm. The prevalence of chronic glaucoma is estimated to be 1.44% (95% CI: 0.94-1.94) in Tehran residents older than 40 years of age.30 The Tehran Eye Study reported an IOP higher than 21 mmHg in only about 0.9% of the population aged more than 40.31 Our screening yielded 6 positive glaucoma cases among 124 studied subjects which amounts to a frequency of about 4.8%; this is comparable to the frequency of glaucoma in Yazd Eye Study but higher than the above mentioned estimate in Tehran residents.31,32 The difference could be due to using stricter criteria and combining diagnostic tests at different steps, which allows the diagnosis of glaucoma along its continuum even in preclinical stages. In this regard, we believe that the likelihood of having had a significant false negative rate is low and that the accuracy of our screening algorithm should therefore be high.

The predictive value of a test for glaucoma depends on two factors: the investigation’s performance in terms of sensitivity and specificity (which in turn depend on definitions and cutoff values), and the prevalence of glaucoma in the studied population.10 Moreover, investigations will have different levels and accuracy depending on the way they are applied, e.g. single versus combined or simultaneous versus consecutive, and by the level of expertise employed.33,34 This is a very complicated situation for glaucoma screening as we have to combine examinations and tests.18,35

It has been recognized that tonometry alone is inadequate for glaucoma screening owing to the poor balance between its sensitivity and specificity.4,36 For instance, an IOP of 21 mmHg or lower as the definition of normality is only 47% sensitive but 92.5% specific. Corneal thickness has gained popularity in the work-up for glaucoma and has now preceded diurnal IOP measurements. In our study, adjusted IOP generally gave a significantly higher estimation and we had twice more abnormal IOP readings. This, in effect, increased the sensitivity of IOP in our protocol. It should be noted that in clinical frameworks, as compared to community settings, low specificity is less of a problem as further assessment of suspected individuals with more valid tests (such as retinal nerve fiber layer imaging in our study) is readily available10 and referrals generally have a more substantive risk profile for glaucoma. We employed stricter cut-offs for VCDR (0.4 versus the common 0.5) and
VCDR asymmetry (0.15 versus 0.2) too; this also improves sensitivity.

In our study, diagnostic evaluations were carried out in collaboration with a glaucoma subspecialist. In suspicious cases, we used the GDx imaging system for diagnosis of early or pre-perimetric glaucoma. However, it has recently been shown that the use of GDx as a screening tool is hampered by high false positive results. Therefore it is advisable to incorporate other accurate objective retinal imaging modalities (i.e. stereoscopic disc photography and confocal scanning laser imaging) in screening algorithms instead of, or in conjunction with GDx for glaucoma screening.

It should be noted that Pentacam HR was chosen for some research purposes other than corneal thickness measurement alone. Pachymetry can be conducted by simpler and less costly methods.

We would like to reiterate the purpose of the clinical screening for glaucoma that is to detect glaucoma in subjects “without a complaint of visual loss”; diagnosing glaucoma in someone who presents with visual loss is not screening. Findings and decisions on the applicability of our algorithm (or its equivalents) require verification through more extensive and comprehensive screening studies. We believe such an algorithm is best applicable to eye care centers.

In summary, we demonstrated how using a formal screening approach in subjects without any complaint of visual loss led to detection of new glaucoma cases. Negative predictive value and likelihood ratio, and the overall accuracy of such protocols should be appraised, especially in routine referrals at eye care centers. Until the time an ideal single diagnostic test is developed, performance of glaucoma screening and diagnosis can be enhanced through incorporating a combination of eye examinations and tests into practice algorithms.

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Conflicts of Interest

None.

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