Research Methodology

Population-Based Screening Versus Case Detection

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India has a large burden of blindness and population-based screening is a strategy commonly employed to detect disease and prevent morbidity. However, not all diseases are amenable to screening. This communication examines the issue of "population-based screening" versus "case detection" in the Indian scenario. Using the example of glaucoma, it demonstrates that given the poor infrastructure, for a "rare" disease, case detection is more effective than population-based screening.

Key Words: Population-based screening, case detection, positive predictive value, glaucoma, diabetic retinopathy

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India is one of the most populous regions of the world. Any health problem afflicting its inhabitants will therefore be a significant cause of morbidity, on a global scale. The question of screening the population for diseases capable of causing such morbidity is obviously very emotive. All of us wish to alleviate human suffering; it somehow goes against the grain to sit back and wait for patients to come to us for treatment when we can "screen" the population to detect disease at an earlier and perhaps more treatable stage, provided of course that the screening is effective and harmless. This article examines the issue of screening the population for ophthalmic disease. It is based on guidelines being prepared for the South East Asia Glaucoma Interest Group and the Asia Oceanic Glaucoma Society. We have used glaucoma as an example, but the arguments are equally applicable to conditions like diabetic retinopathy.

It is estimated that there are 12 million bilaterally blind in India.[1] The common causes for blindness are cataract, glaucoma and corneal diseases.[2] Glaucoma, a chronic, progressive optic neuropathy, is an important cause of blindness. It is estimated that 13% of the blindness in India is caused by glaucoma and that the disease affects 12 million Indians.[2] This large burden raises the question of screening the population to detect and initiate prompt treatment for glaucoma.

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Criteria for population-based screening

The World Health Organization recommends that certain defined criteria be fulfilled before any population-based screening is undertaken. These criteria are listed below.[3]

1. The disease must be an important public health problem.
2. There must be a recognizable latent or early stage, during which persons with the disease can be identified before symptoms develop.
3. There must be an appropriate, acceptable and reasonably accurate screening test.
4. There must be an accepted and effective treatment for patients with the disease that must be more effective at preventing morbidity when initiated in the early asymptomatic stage than when begun in the later symptomatic stages of the disease.
5. The cost of case finding must be economically balanced in relation to possible expenditure on medical care as a whole.

Other questions that need to be asked before embarking on any screening program are listed below.[4,5]

1. Does early diagnosis lead to improved clinical outcomes in terms of visual function and quality of life?
2. Can the health system cope with the additional clinical time and resources required to confirm the diagnosis and provide longterm care for those who screen positive for a chronic disease such as glaucoma?[3] Is the incidental harm done by screening and by the information (correct or otherwise) small in relation to the total benefits from the screening-assessment-treatment system?[4] Will the patients in whom early diagnosis is

achieved comply with subsequent recommendations and treatment regimens?

3. Are the cost, accuracy, and acceptability of the screening tests adequate for our purpose?

It is also important to remember that case finding should be a continuing process and not a "once and for all project". This obviously adds to the complexity.

Glaucoma (and diabetic retinopathy) does fit some of the criteria required for screening but others are more problematic. It is likely that the health systems of only the most developed countries in the region may have the ability to cope with the additional clinical time and resources required. The question of screening the population for glaucoma is therefore not clear-cut. What then is the best strategy to detect glaucoma?

In order to evaluate the issue of "screening" for glaucoma it is important to review some definitions:

Definitions

In this document, ***screening*** refers to ***population-based*** detection of glaucoma. ***Case detection*** (opportunistic screening) refers to the active detection of glaucoma when patients visit clinics and hospitals for "*other reasons*"**.** ***Prevalence*** of a disease is the proportion of patients with the target disorder (glaucoma) in the population tested. The ***sensitivity*** is the ability of a test to correctly identify those who have glaucoma (true positives). The ***specificity*** is the ability of a test to correctly identify those who do not have glaucoma (true negatives or normal). The ***positive predictive value*** of a test is the proportion of patients with positive results who actually have glaucoma. The ***negative predictive value*** is the proportion of patients with negative test results who do not have glaucoma.

The predictive value of a test is dependent on the prevalence of glaucoma in the tested population. As shown in the Figure, when all other factors remain constant, the positive predictive value (PPV) will increase with increasing prevalence. With a low prevalence of glaucoma, most of those who test positive will in fact be false positives.

In order to increase the effectivity of the tests, the prevalence of glaucoma in the population to be tested must be reasonably high. We can "increase" the prevalence of glaucoma by targeting high-risk groups such as the elderly, persons with family history of glaucoma, diabetics, myopic, etc.

Tests used for screening

Detecting early glaucoma is ideal, but requires a sensitive test. A test that is sensitive enough to detect early disease usually leads to many false positives. For screening, a test should have a reasonably high sensitivity with as high a specificity as possible. Prevent Blindness America suggests 95-98% specificity and 85% sensitivity for moderate to severe glaucoma.[6] For screening purposes it may be better to target the moderate and advanced cases that require urgent treatment. Diagnostic tests will have a higher sensitivity and specificity in such cases.

The tests for screening / case detection are described below.

Primary open angle glaucoma (POAG)

Tonometry

Tonometry has poor sensitivity and specificity for the detection of glaucoma. For the detection of POAG, at a cutoff of > 21mm Hg, applanation tonometry has a sensitivity of 47.1% and specificity of 92.4%.[7] Half of all patients with POAG have IOPs below 22mmHg at a single screening. Further, many individuals with raised IOPs may never develop optic nerve damage. IOP measurement alone is an inefficient tool to screen populations for glaucoma.

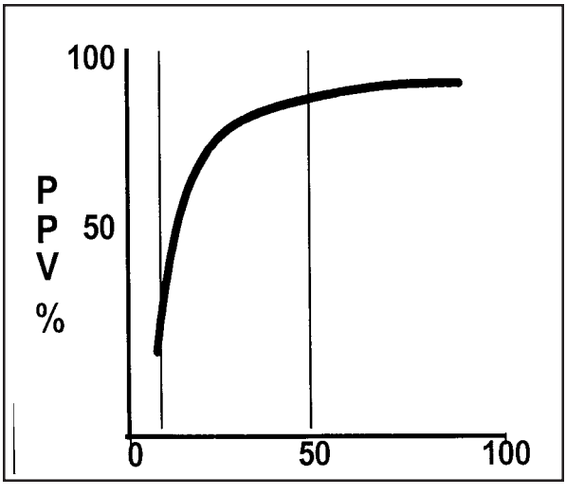
Perimetry

The gold standard in perimetry is conventional white-on-white automated perimetry. The sensitivity and specificity of automated perimetry for screening is 97% and 84% respectively.[8] The test can be made more specific or sensitive but despite the improvements in testing strategies, it is still a time consuming and laborious screening device.

Frequency Doubling Perimetry (FDP) is a rapid and relatively inexpensive test that can accurately detect established glaucoma. FDP has been reported to have a sensitivity of 90 – 94% and a specificity of 91% – 96%.[9,10]

Disc and Nerve Fiber layer examination

Glaucoma is essentially an optic neuropathy and the key to diagnosis rests on examination of the disc and nerve



Positive predictive value increases with increase in disease prevalence

fibre layer. While this is best performed using slitlamp biomicroscopy with 60, 78 or 90 D lenses, a direct ophthalmoscope is a reasonable alternative. The sensitivity and specificity of optic nerve head evaluation depends on the technique used and the diagnostic criteria for glaucoma. Using a cup-to-disc ratio of 0.55 as a cut off, the sensitivity and specificity are 59% and 73% respectively.[11] Inter-observer agreement of disc examination by clinical methods or fundus photographs is low.

The newer imaging techniques for the disc and nerve fibre layer are promising, but are expensive and have not been validated.

In the Baltimore survey, various combinations of disc parameters, IOP, and family history had only moderate sensitivity (49-66%) and specificity (79-87%) for glaucoma.[12]

Primary angle closure glaucoma (PACG)

Population-based studies from the West have shown the prevalence of POAG at five fold greater than PACG.[12,13] It is, however, estimated that half the glaucoma in the world is caused by angle closure.[14] In order to be effective, any screening / case detection initiative has to include methods to detect angle closure. Tonometry will only detect angle closures that have a raised IOP. The structural and functional tests described for POAG (Optic disc examination, Perimetry) will only detect angle closure that has damaged the disc or visual field. However, as approximately 75% of subjects with PACG in Asia have optic nerve damage Screening strategies that detect functional damage in POAG may also be suitable for PACG.[15] Such tests will **neither** detect eyes without functional damage, nor eyes at risk for angle closure.

The ideal way to identify angle closure and eyes at risk is to examine the angle using a gonioscope.[16] The required clinical expertise and instrumentation required render gonioscopy inappropriate for screening.[17]

Methods to identify eyes at risk of angle closure include *anterior chamber depth as well as anterior chamber depth*/axial length ratio. The sensitivity and specificity of these techniques do not make them appropriate for screening.[18] Furthermore, they require expensive instrumentation and trained technicians.

Other easier techniques include the flashlight test and the van Herick test. In the flashlight test a light is shone from the temporal side onto the cornea, parallel but anterior to the iris. A shadow on the nasal limbus identifies an eye with a shallow anterior chamber, at risk for closure. The sensitivity of the flashlight test is 80-86% and specificity is 69-70%.[19,20]

The van Herick test uses a slit beam to compare the peripheral anterior chamber depth to the thickness of the cornea. The sensitivity and specificity of the test is 61.9% and 89.3% respectively.[19] Expressing the test in decimals yields similar results.[20] 89.3% is a reasonably high specificity, but does not meet the recommendations of Prevent Blindness America. It is important to remember that the flashlight and van Herick tests do not detect angle closure, but occludable angles, which are only a risk factor for angle closure. This distinction becomes important because only a minority of occludable angles progress to angle closure. Using the van Herick test for screening will result in too many false positives[21] and the flashlight test is worse.[19]

It is possible to obtain a higher specificity (or sensitivity) by using tests in combination. If the van Herick test is positive and the IOP is raised, the specificity improves to 99.3%.[21] The sensitivity will decrease. However, as far as a population-based screening strategy is concerned, if the IOP is raised and the van Herick test is positive, the specificity is high enough to actually treat the patient as having angle closure. The resultant senstitivty and specificity for any combination of tests can be calculated.[21]

Problems with population-based screening [22]

1. When a patient comes to see us in the clinic, they are seeking us out; we treat them to the best of our ability, but without a guarantee for cure. In screening, we are seeking them out; there is an implied pledge that we are going to make them better.
2. When we seek out patients we are obliged to establish a diagnosis and treat those who have glaucoma. If we do not have the infrastructure to establish diagnosis and provide appropriate treatment, screening is not justified. The diagnosis here requires the state of the art as detailed in the examination section below. Certainly the patient cannot be "confirmed" to have disease by using only techniques used for "screening".
3. The patients who turn out to be false positives carry the burden of being labeled. The consequences can be severe. Normal children misdiagnosed as having heart disease were found to be as handicapped as children who had the disease.[23] In fact, due to the false positives, the amount of disability from cardiac "non-disease" greatly exceeded that from actual heart disease. Similarly, delivering a diagnosis of glaucoma or glaucoma suspect has a lot of adverse psychological implications.[24,25]
4. Finally, patients who actually have the disease but have tested negative are given a clean bill of health, which can be dangerous.

The above arguments apply even when high-risk groups like the elderly or residents of old-age homes are targeted for screening.

Most regions in the country may not have the requisite infrastructure to follow up and categorize test positives or even treat them appropriately. Glaucoma management, both medical as well as surgical is very intensive. In this situation, it is perhaps inappropriate to screen the general population. Also, we must

remember that in order to be effective, such screening cannot be a one-time affair; even developed countries can probably ill afford to screen the population at large for glaucoma and handle the burden of further testing, treating and follow up.

Case detection (Opportunistic screening)

As opposed to population-based screening, case detection relies on detection of disease (in the present case, glaucoma) in patients who present to our offices for various complaints.

Most elderly patients, diabetics and myopes (all at risk for glaucoma), visit the offices of ophthalmologists and optometrists for other eye care needs. They also visit physicians for medical needs. In this scenario, where the prevalence of glaucoma is higher, most of the tests described above – tonometry, ophthalmoscopy and perimetry – have a high positive predictive value. Gonioscopy is the gold standard for the diagnosis of PACG. The general physician too can play an important role in the diagnosis of open angle glaucoma. Ophthalmoscopy and FDP are feasible in a physician's office (as much as blood pressure measurements for detection of hypertension are feasible in our offices).

Recommendations

Population-based screening

This is not recommended as a strategy. Population-based screening is especially inappropriate for developing countries without an adequate infra-structure. Adequate infrastructure here implies the availability of expertise (trained ophthalmologist), time and instrumentation required to confirm the diagnosis amongst test positives in an appropriately modern manner. It also means the availability of expertise (trained surgeons) and instrumentation to appropriately treat those in whom the diagnosis is confirmed. The operative word is "appropriate" and implies modern preferred practice. The requirements for the diagnosis and management are covered in the relevant sections.

Each region will need to make a decision on population-based screening based on an assessment of the ground reality. While some more developed countries may opt to target high-risk groups for screening, this looks like a distant objective in India.

Case detection

To be effective, any person over the age of 35 who seeks ophthalmic attention for any reason should have a comprehensive ophthalmic examination. As far as the diagnosis of glaucoma is concerned, this would include the following: (Note: the tests are not listed in the order they may be performed)

1. *Tonometry*
   Ideal: Applanation tonometry
   Less than ideal: Pneumotonometer or Schiotz tonometer
2. *Dilated evaluation of the optic disc*
   Ideal: Dilated stereoscopic evaluation by slitlamp biomicroscopy, fundus photography.
   Acceptable : Direct ophthalmoscope.
3. *Slit lamp biomicroscopy and van-Herick test.*
4. *Gonioscopy.*
   Ideal: indentation gonioscopy using a Sussman, Zeiss or Posner lens.
   Acceptable: Goldman single or two-mirror lens with "manipulation".[19]
   Some patients cannot tolerate an indentation examination and others cannot tolerate a Goldmann lens. It is probably desirable to have both types of gonioscopes available and carry out a dynamic examination.
   Gonioscopy is mandatory for every glaucoma suspect, irrespective of whether the suspicion is based on a raised IOP, optic disc, or visual field findings. The flashlight and/or van Herick tests are not appropriate tools to diagnose angle closure. A positive flashlight or van Herick test requires confirmation by gonioscopy. It may however be logistically impossible to gonioscope everybody in a clinic. The following guideline may help:
   If the flashlight test is negative (less than 1/3 of the iris on the nasal side of the pupil covered by shadow) and the van Herick test is negative (an anterior chamber depth of more than 1/4 thickness of the peripheral cornea), an occludable angle is highly unlikely.[19] In this situation a gonioscopy for the purpose of ruling out an occludable angle may not be necessary.
5. *Visual field examination:* If the IOP is > 21 mmHg and/or the disc is suspicious, the patient should undergo a visual field examination.
   Ideal: A full threshold test using a calibrated white-on-white automated perimeter or Goldman perimetry. A trained technician must perform the latter.
   Acceptable: Frequency doubling perimeter, Henson's visual field screener, or a Bjerrums screen (used by a trained, experienced person).

Summary and Conclusions

Currently, the optimal method for detection of individuals with glaucoma is periodic routine comprehensive eye examinations. The feasibility of this would however depend on the current state of the health care system in the individual country. In lieu of the ideal, case detection should be relied on.

While the example used in this article is glaucoma, the reader will immediately realise that the arguments are equally applicable to other ophthalmic diseases that are relatively "rare" in the general population. We can use diabetic retinopathy as an example. To prevent any

misunderstanding, we will state the obvious: All diabetics require a fundus examination. Now let usconsider the screening for diabetic retinopathy:

Diabetes affects 4% of the population.[26] Diabetic retinopathy occurs in 23 % of diabetics, but only 1.78% of the general population.[27] As in "screening" for glaucoma, it is reasonable to try and detect moderate and advanced diabetic retinopathy. About 10% of the diabetics (0.2% of the general population) will have "sight threatening" retinopathy that requires priority detection.[24] Glaucoma has a higher prevalence than diabetic retinopathy (2.5-4%) [28-30] and is still not suitable for population-based screening. All the arguments used in the population based screening for glaucoma apply to diabetic retinopathy as well. The strategies for detection are also similar.

Currently for India the approach to problem of glaucoma, diabetic retinopathy (and other similarly "less common" ophthalmic diseases) should probably be case detection. To be effective, ophthalmologists, optometrists, diabetologists, physicians and other health care personnel, must all be involved in such case detection.

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