Prevalence of Increased Intraocular Pressure and Optic Disk Cupping: Multicenter Glaucoma Screening in Israel during the 2009 and 2010 World Glaucoma Weeks

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ABSTRACT: Background: Early detection of glaucoma enables early initiation of treatment. Screening populations at risk is likely to help achieve this goal. Objectives: To increase public awareness regarding early detection of glaucoma, and estimate the prevalence of increased intraocular pressure (IOP) and optic disk cupping in the screened population. Methods: A public awareness campaign was carried out in Israel during the 2009 and 2010 World Glaucoma Week, culminating each year in a one-day, free-of-charge screening of individuals in 13 outreach public locations. Screening was performed by 45 ophthalmologists and included a brief medical history, slit-lamp exam with measurement of intraocular pressure (IOP), and evaluation of cup/disk ratio. Results: A total of 2560 individuals were screened; the mean age was 59 ± 13 years. IOP ≥ 21 mmHg was found in 4.8%, and 12.3% had cupping ≥ 0.5. IOP ≥ 21 mmHg together with cupping ≥ 0.5 were present in 1.4% and this rate increased with age: 3.7% of cases in the age group ≥ 70 years compared to 1% and 0.6% in the age groups 50–69 and < 50 years, respectively (P < 0.001). Likewise, the prevalence of cupping ≥ 0.7 and of IOP ≥ 24 mmHg increased significantly with age. The prevalence of IOP ≥ 21 mmHg increased in cases with a family history of glaucoma in first-degree relatives (10.5% compared to 3.9%, P < 0.001). The prevalence of IOP ≥ 21 mmHg was also increased in diabetic patients (8.3% vs. 4.3% in non-diabetics, P = 0.002). Further ophthalmologic evaluation was recommended to 13% of the screened individuals. Conclusions: Outreach screening for glaucoma is a valuable tool for detecting glaucoma, pre-perimetric glaucoma, or ocular hypertension in a meaningful number of previously undiagnosed cases. Yet, cost-effectiveness issues should also be considered. The yield of such screening increases with age and seems to be most advantageous in cases with diabetes or a family history of glaucoma.

KEY WORDS: glaucoma, intraocular pressure (IOP), cup/disk ratio, screening

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Early detection of glaucoma enables initiation of therapy at an early stage and may delay disease progression [1]. However, many cases are diagnosed at a late stage of the disease when significant optic nerve damage has already occurred. In the Thessaloniki Eye Study [2] the lack of regular visits to an ophthalmologist was a major factor in undiagnosed open angle glaucoma. The Costs of Glaucoma Study Group concluded that patients diagnosed at higher baseline stages incurred greater costs [3]. However, no randomized controlled trials of screening have been performed and cost-effectiveness studies of screening show inconsistent results [4].

An increase in public awareness combined with screening large populations at risk may help to detect undiagnosed ocular hypertension, pre-perimetric glaucoma, or glaucoma at an earlier stage in a significant number of cases. Such a campaign was initiated in Israel in conjunction with the World Glaucoma Week of 2009 and 2010.

METHODS

A national public awareness campaign was initiated by the Israel Glaucoma Society and carried out in both the electronic and paper media in Israel during the World Glaucoma Week of 2009 and 2010, culminating each year in a one-day, free-of-charge screening of individuals in 13 outreach public locations throughout the country. Screening was performed by 45 ophthalmologists, the Israel Glaucoma Screening Group. It comprised a brief medical history, slit-lamp examination including intraocular pressure and anterior chamber depth evaluation, and non-mydriatic fundus exam with

evaluation of the cup/disk ratio. Both eyes were examined in each case. In cases with differences between the right and left eyes, the more abnormal result was considered for this evaluation. Each team comprised at least two ophthalmologists and a secretary. All subjects volunteered to participate in the national screening day. Equipment was donated for one day by ophthalmology departments of the area hospitals or by local distributors. Screening locations were in the lobbies of major general hospitals or shopping malls.

All individuals interested in free-of-charge screening were examined. Cases with prior diagnosis of glaucoma or ocular hypertension were excluded. The results and their meaning were explained to the screened individuals upon completion of the examination. When necessary, further examination at an ophthalmology clinic was recommended.

Data were collected at a later date from all 13 locations. Retrospective analysis of these data was performed initially by descriptive statistics. Further analyses comparing categorical variables of IOP and cupping in different age groups and in males and females, and comparing these categorical variables in cases with or without diabetes, family history of glaucoma or myopia were performed with chi-square analysis.

RESULTS

A total of 2560 individuals were screened, 1346 females and 1214 males. All were older than 30 years and their mean age was 59 ± 13. OHT (IOP ≥ 21 mmHg) was found in 124 individuals (4.8%), and 316 (12.3%) had cupping ≥ 0.5 [Table 1]. In cases with differences between the right and left eyes, the more abnormal result was considered for this evaluation. Cases with both OHT and cupping, apparently suggestive of glaucoma or pre-perimetric glaucoma, were less common (37 cases, 1.4%).

The prevalence of OHT and of cupping increased significantly with age [Table 2]. In the older age group (70 years and above, n=520) cupping was observed in 17.1%, OHT in 8.5%, and both abnormalities in 3.6% of screened individuals.

Individuals with a family history of glaucoma in first-degree relatives (n=372) had an increased prevalence of IOP ≥ 21 mmHg (10.5% compared to 3.9% in individuals with no family history, P < 0.001). Increased prevalence of cupping ≥ 0.5 was also observed in individuals with a family history of glaucoma in first-degree relatives (15.6% compared to 11.8% in individuals with no family history, P = 0.048). Differences in prevalence of increased IOP and of cupping between individuals with a family history of glaucoma and those with no family history increased with age [Table 3]. Individuals in the age group 50–69 had increased prevalence of IOP ≥ 21 mmHg if they had a family history of glaucoma, compared to those with no family history (9.5% and 3.7%, respectively, P < 0.001). In those aged 70 years and above, 25% with a family history of glaucoma had IOP ≥ 21 mmHg as compared to only 6.9% of individuals with no family history (P < 0.001). Cupping was also more prevalent in individuals with a family history of glaucoma in this age group (31.8% and 15.8%, respectively, P = 0.013).

Diabetes was reported by 362 of the screened individuals. The prevalence of IOP ≥ 21 mmHg was increased in those

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Table 1. Prevalence of elevated IOP and enlarged cupping in the screened population (n=2,560)

<table>
<thead>
<tr>
<th>IOP ≥ 21 mmHg</th>
<th>No. of screened individuals (%), CI</th>
</tr>
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<tbody>
<tr>
<td>214 (4.8, 4.1–5.7)</td>
<td></td>
</tr>
<tr>
<td>39 (1.5, 1.1–2.1)</td>
<td></td>
</tr>
<tr>
<td>316 (12.3, 11.1–13.7)</td>
<td></td>
</tr>
<tr>
<td>122 (4.8, 4.0–5.7)</td>
<td></td>
</tr>
<tr>
<td>37 (1.4, 1.0–2.0)</td>
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</tbody>
</table>

In cases with differences between the right and left eyes, the more abnormal result was considered for this evaluation. CI = 95% confidence interval, C/D = cup/disk ratio, IOP = intraocular pressure

Table 2. Cases with elevated IOP and/or enlarged cupping in different age groups

<table>
<thead>
<tr>
<th>Age group (yr)</th>
<th>No. of cases</th>
<th>IOP ≥ 21, n (%)</th>
<th>C/D ≥ 0.5, n (%)</th>
<th>C/D ≥ 0.7, n (%)</th>
<th>C/D ≥ 0.5 and IOP ≥ 21, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>646</td>
<td>15 (2.3)</td>
<td>49 (7.6)</td>
<td>23 (3.6)</td>
<td>4 (0.6)</td>
</tr>
<tr>
<td>50–69</td>
<td>1394</td>
<td>65 (4.7)</td>
<td>178 (12.8)</td>
<td>57 (4.1)</td>
<td>14 (1.0)</td>
</tr>
<tr>
<td>≥ 70</td>
<td>520</td>
<td>44 (8.5)</td>
<td>89 (17.1)</td>
<td>42 (8.1)</td>
<td>19 (3.6)</td>
</tr>
</tbody>
</table>

Table 3. Cases with elevated IOP and/or enlarged cupping in relation to family history of glaucoma in first-degree relatives, in each age group

<table>
<thead>
<tr>
<th>Age group (yr)</th>
<th>Family history</th>
<th>FH</th>
<th>No FH</th>
<th>FH</th>
<th>No FH</th>
<th>FH</th>
<th>No FH</th>
<th>FH</th>
<th>No FH</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>96</td>
<td>6 (6.2)</td>
<td>9 (1.6)</td>
<td>22 (9.5)</td>
<td>43 (3.7)</td>
<td>11 (25.0)</td>
<td>33 (6.9)</td>
<td>39 (10.9)</td>
<td>85 (23.9)</td>
</tr>
<tr>
<td>50–69</td>
<td>550</td>
<td>23 (4.2)</td>
<td>43 (7.8)</td>
<td>38 (6.4)</td>
<td>140 (12.0)</td>
<td>14 (31.8)</td>
<td>75 (15.8)</td>
<td>58 (15.8)</td>
<td>258 (44.8)</td>
</tr>
<tr>
<td>≥ 70</td>
<td>1182</td>
<td>44 (3.7)</td>
<td>75 (6.4)</td>
<td>44 (3.7)</td>
<td>75 (6.4)</td>
<td>14 (31.8)</td>
<td>75 (15.8)</td>
<td>58 (15.8)</td>
<td>258 (44.8)</td>
</tr>
</tbody>
</table>

C/D = cup/disk ratio, FH = family history of glaucoma in first-degree relatives, IOP = intraocular pressure

IOP = intraocular pressure
OHT = ocular hypertension
cases (8.3% compared to 4.3% in non-diabetics, \( P = 0.002 \)). However, there was no difference in the prevalence of cupping between cases with or without diabetes. There were no significant differences in the prevalence of increased IOP or enlarged cupping between men and women and between individuals with or without myopia.

Further ophthalmologic evaluation was recommended to 335 of the screened individuals (13%). As this was not a prospective study, no formal guidelines were designed to suggest further evaluation and this was left to the discretion of the examining ophthalmologist. Yet, following retrospective analysis of the data it appears that further evaluation was recommended to most individuals with increased IOP and/or enlarged cupping.

**DISCUSSION**

Our report focuses on the ability of events such as this public awareness and screening campaign to detect cases with previously undiagnosed glaucoma, OHT, or abnormal cupping in a meaningful number of cases. OHT, pre-perimetric glaucoma or glaucoma were suspected in more than 10% of the screened individuals. As a result of the screening campaign one of eight screened individuals was referred for further evaluation. The prevalence of cupping was more common than OHT (12.3% and 4.8%, respectively). This may represent healthy individuals with physiological cupping but may also be a sign of normal tension glaucoma, necessitating further evaluation.

For the purpose of screening, the disk pathology was evaluated solely by the cusp/disk ratio. Other disk changes were not evaluated in this screening process. It should be noted that some of these cases with cupping and normal IOP may represent primary open angle glaucoma that had IOP of 21 mmHg at the time of the screening examination. Indeed, in the Rotterdam Eye Study and the Beaver Dam Eye Study, 39% and 32% respectively of primary OAG patients had IOPs of 21 mmHg or lower [5,6].

Much effort is invested in screening for glaucoma. The question whether this effort is worthwhile has been addressed by several investigators. In 2008 Hernández et al. [7] reported a systematic review of studies regarding the cost-effectiveness of screening for glaucoma. They found only four studies, all prior to the year 2000, from which they were able to calculate incremental cost-effectiveness ratios based on data provided in those studies. The issues of interest were data on costs with regard to: a) cases and years of visual impairment prevented, b) cases of blindness prevented, and c) cases of OAG detected. They concluded that there was insufficient economic evidence on which to base recommendations regarding screening for OAG.

The Salzburg-Moorfields Collaborative Glaucoma Study performed a complete ophthalmologic examination on 4864 subjects during a study period of 98 months in a clinic setup [8]. A total of 9427 examinations and verification checks were performed. Based on estimated costs per visit (€123 per initial examination and €95 per follow-up examination), it was estimated that the costs for detecting a new case of glaucoma were €7250 for definite primary OAG, €4250 for early primary OAG, and €1450 for primary OAG-suspect. Cost-effectiveness is dependent on a multitude of parameters. Costs differ significantly among various countries. Effectiveness is likely to increase if screening is performed on more susceptible populations, such as family members of patients with glaucoma. In this report we disregarded the cost-effectiveness issue as no cost could be attributed to this screening day; furthermore, no follow-up data are currently available on these cases. Disregarding the cost-effectiveness question, we found that the yield of such screening increases with age, but it should be noted that Tuck and Crick [9] found that screening of the younger age group (40–60 years) was about as economical as for older people when life expectancy was taken into account.

Glaucoma screening by a mobile unit in Israel was described 12 years ago [10]. In that report the prevalence of OHT (defined as IOP ≥ 22 mmHg) was 8%, and the prevalence of OHT and “disk damage” (cup/disk ratio not specified) was 0.8% for the whole group. Similar to the age-specific prevalence rates in our study, this rate gradually increased with aging, from 1.2% in the age group 40–60 years to 3.6% in the age group 70–80 years and 10% in older individuals. Diabetes, a family history of glaucoma, and myopia were more common in these cases compared with individuals without OHT and disk damage.

Regarding the association with diabetes, in our study the prevalence of IOP ≥ 21 mmHg was higher in cases with diabetes (8.3% compared to 4.3% in non-diabetics, \( P = 0.002 \)). However, there was no difference in the prevalence of cupping. Increased risk of glaucoma in diabetic patients was recently reported in the Thessaloniki Eye Study [11] and by Goldacre et al. [12] using large epidemiological datasets, although no such association was found in previous studies (the Barbados Eye Study, the Beaver Dam Eye Study, the Rotterdam Eye Study, the European Glaucoma Prevention Study, and the combined analysis of the Ocular Hypertension Treatment study and the European Glaucoma Prevention Study) [5,6,13-15]. We did not find significant differences in the prevalence of increased IOP or increased cupping between individuals with or without myopia, but a recent meta-analysis of observational studies concluded that individuals with myopia have an increased risk of developing OAG [16].

In conclusion, outreach screening for glaucoma is a valuable tool for detecting glaucoma, pre-perimetric glaucoma, or ocular hypertension in a significant number of previously undiagnosed
cases. The yield of such screening increases with age, and seems to be most advantageous in cases with diabetes or a family history of glaucoma. Yet, cost-effectiveness issues should also be considered when designing such screening programs.

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References

Capsule
The heart needs blood vessels, too
For the newborn heart to grow quickly, the heart’s own blood vessels must grow as well. Researchers have assumed that preexisting fetal coronary vessels expand to cause this postnatal coronary vascular growth. Instead, Tian and collaborators show that, for the most part, brand-new blood vessels form within the neonatal heart (see the Perspective by Burns and Burns). This ability to produce new coronary blood vessels after birth may one day help researchers work out how to promote cardiovascular regeneration after injury or disease.

Science 2014; 345: 90
Eitan Israeli

Capsule
Comprehensive molecular profiling of lung adenocarcinoma
Adenocarcinoma of the lung is the leading cause of cancer death worldwide. The Cancer Genome Atlas Research Network report molecular profiling of 230 resected lung adenocarcinomas using messenger RNA, microRNA and DNA sequencing integrated with copy number, methylation and proteomic analyses. High rates of somatic mutation were seen (mean 8.9 mutations per megabase). Eighteen genes were statistically significantly mutated, including RIT1 activating mutations and newly described loss-of-function MGA mutations which are mutually exclusive with focal MYC amplification. EGFR mutations were more frequent in female patients, whereas mutations in RBM10 were more common in males. Aberrations in NFI, MET, ERBB2 and RIT1 occurred in 13% of cases and were enriched in samples otherwise lacking an activated oncogene, suggesting a driver role for these events in certain tumors. DNA and mRNA sequence from the same tumor highlighted splicing alterations driven by somatic genomic changes, including exon 14 skipping in MET mRNA in 4% of cases. MAPK and PI(3) K pathway activity, when measured at the protein level, was explained by known mutations in only a fraction of cases, suggesting additional, unexplained mechanisms of pathway activation. These data establish a foundation for classification and further investigations of lung adenocarcinoma molecular pathogenesis.

Nature 2014; 511: 543
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