Genetic Risk of Primary Open-angle Glaucoma

Population-Based Familial Aggregation Study

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Objectives: To study familial aggregation of primary open-angle glaucoma in a general population and to determine the absolute and relative risks for first-degree relatives.

Methods: First-degree relatives of patients with glaucoma (n = 48) and control subjects (n = 155) from the population-based Rotterdam Study underwent a standardized examination, including perimetry.

Main Outcome Measures: Intraocular pressure; vertical cup-disc ratio; and the presence of glaucoma, defined as a visual field defect with a cup-disc ratio of 0.7 or higher or asymmetry of 0.3 or higher between both eyes.

Results: The prevalence of glaucoma was 10.4% in siblings of patients, 1.1% in offspring of patients, 0.7% in siblings of controls, and 0% in offspring of controls. Lifetime risk of elevated intraocular pressure in relatives of patients vs relatives of controls was 42.5% vs 6.7%, of enlarged cup-disc ratio was 62.2% vs 16.6%, and of glaucoma was 22.0% vs 2.3%, yielding a risk ratio for glaucoma of 9.2 (95% confidence interval = 1.2-73.9). The population-attributable risk of glaucoma was 16.4%.

Conclusions: In a general population, relatives of patients with glaucoma have a strongly increased risk of glaucoma. Enlarged cup-disc ratio, not intraocular pressure, was the earliest and most prominent feature of familial aggregation. Further studies are needed to disentangle the genetic components of the increased familial risk.


The cause of primary open-angle glaucoma, in this article further referred to as glaucoma, is as yet unknown. This disorder is the second most prevalent cause of incurable blindness in the elderly. Findings from epidemiological studies indicate that apart from high intraocular pressure and age, ethnic origin, diabetes mellitus, and familial history are associated risk factors. Evidence for genetic factors has been found for juvenile-onset glaucoma and for selected families with adult-onset glaucoma. The purpose of this research was to study whether familial aggregation of glaucoma occurs in the general population. We, thereto, selected probands from the population-based Rotterdam Study and determined the presence of glaucoma in their relatives by actual examination using a standardized protocol. We calculated the absolute and relative risks of glaucoma for first-degree relatives and estimated to what extent genetic factors contribute to the overall occurrence of glaucoma.

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As early as 1869, von Graefe mentioned hereditary glaucoma, and in 1941, Duke-Elder described a type of glaucoma that was inherited in a dominant manner and was called familial glaucoma. Since then, many studies have been performed in selected families in which the familial aggregation, inheritance, and mode of transmission of glaucoma were studied. These studies differed significantly in methods and in criteria for the diagnosis of glaucoma, resulting in different conclusions regarding the inheritance. Often, only family history was taken into account, or a limited number of family members were actually ophthalmologically examined. Moreover, most studies were clinic based, which opens the possibility of selection bias related to family history and severity of disease. Although in several studies there was evidence of autosomal-dominant inheritance and familial aggregation, it is not clear whether this accounts for all patients with glaucoma.

The purpose of this research was to study whether familial aggregation of glaucoma occurs in the general population. We, thereto, selected probands from the population-based Rotterdam Study and determined the presence of glaucoma in their relatives by actual examination using a standardized protocol. We calculated the absolute and relative risks of glaucoma for first-degree relatives and estimated to what extent genetic factors contribute to the overall occurrence of glaucoma.

Results

The mean age of patients with glaucoma was 73.8 years, slightly lower than that of...
PARTICIPANTS AND METHODS

STUDY POPULATION

This study was performed as a part of the Rotterdam Study,3,19 a prospective population-based study of determinants and prognoses of severe disabling ophthalmic, cardiovascular, neurologic, and locomotor diseases. The present study was approved by the Medical Ethics Committee of Erasmus University, Rotterdam, the Netherlands. Written informed consent was obtained from all participants.

At the start of the study, all known patients with glaucoma (n = 48) from the baseline phase of the Rotterdam Study4 were asked to participate in the family study. In addition, a random sample of all participants without glaucoma was asked to serve as a control group (n = 155). This group was frequency matched for age in 5-year strata and for sex. All probands were contacted by letter and by telephone and were subsequently visited at their homes. When informed consent was obtained, their first-degree relatives were contacted for an examination. Eligible for this study were all first-degree relatives living in the Netherlands or Belgium.

RESPONSE

The overall response among probands was 88.7% (180 of 203 eligible probands participated). Among patients, 45 (94%) of 48 participated compared with 133 (87.1%) of 155 controls. Among siblings, overall response was 80.1% (209/261). Of the 83 eligible siblings of patients with glaucoma, 67 (81%) participated, as did 142 (79.8%) of 178 siblings of controls (95% confidence interval [CI] = −0.3 to −5.7, adjusted for sex). The mean age of offspring of patients was 42.2 years; they were, on average, 3.5 years younger than offspring of controls (95% CI = −1.3 to −5.7). The overall response among parents was 82.4% (261). Of the 261 eligible relatives, 203 (82.4%) of 247 children of controls. Overall response for all relatives was 82.4%. Reasons for nonresponse did not differ between groups.

MEASUREMENTS

Most family members were examined in the research center of the Rotterdam Study. Participants who were homebound were examined at their homes using portable examination equipment, including a “portable” perimeter (Humphrey Visual Field Analyzer II, model 750, Humphrey Systems, Dublin, Calif). Family members of patients and controls underwent the same examinations.

Intraocular pressure was measured 3 times (with a Goldmann applanation tonometer), and the median of these 3 consecutive measurements was taken. Intraocular pressure was considered to be elevated when it was above 21 mm Hg or when therapy to lower intraocular pressure was in progress. The visual field was examined with the portable perimeter using the central 24-2 full-threshold program. After administration of mydriatic eyedrops, simultaneous stereofundus transparencies with a fixed stereoaangle (model TRC-SS2, Topcon Optical Co, Tokyo, Japan) were made from the optic disc, and ophthalmoscopy was performed to examine the optic nerve head.

All stereoscopic optic disc transparencies were used for automated assessment of the optic nerve head characteristics with a digital image analyzer (Imagenet 2000 system, Topcon Optical Co). This system measured 3-dimensional topography data based on parallax shifts between both pictures on the stereoscopic slide. Use of the digital image analyzer enhanced the standardization and precision of the optic disc measurements and reduced interobserver variability and measurement bias.21,22 The vertical cup-disc ratio, as measured with a digital image analyzer, differed between groups.

controls (76.7 years; P = .01). The percentage of women in the patient group vs the control group was similar (55% vs 48%, age-adjusted P = .40). There were no significant differences in the number of first-degree relatives between both groups (P = .95). Controls had slightly more siblings (P = .43), whereas patients had a slightly higher number of offspring (P = .32). The proportion of deceased relatives was similar in both groups (P = .99).

The mean age of siblings of patients was 72.3 years (Table 1); they were, on average, 3.0 years younger than siblings of controls (95% confidence interval [CI] = −0.3 to −5.7, adjusted for sex). The mean age of offspring of patients was 42.2 years; they were, on average, 3.5 years younger than offspring of controls (95% CI = −1.3 to −5.7).

Siblings of patients had significantly higher intraocular pressures and cup-disc ratios than siblings of controls (Table 2). Therapy to lower intraocular pressure was significantly more frequent in siblings of patients. In offspring, findings were similar for mean intraocular pressure and cup-disc ratio, but differences were smaller and only statistically significant for intraocular pressure. The prevalence of glaucoma in siblings of patients was 10.4% (n = 6) compared with 0.7% (n = 1) in siblings of controls (Table 3) (prevalence odds ratio = 14.7, 95% CI = 1.7-130.0, adjusted for age and sex). The prevalence of glaucoma in offspring of patients was 1.1% (n = 1), and this was not present among offspring of controls. These differences were independent of diabetes mellitus or hypertension (Table 3 and Table 4). We found no statistical evidence for interaction between familial risk and diabetes mellitus or hypertension (data not shown).

Figure 1 and Figure 2 show the lifetime risks of elevated intraocular pressure and enlarged cup-disc ratio in relatives of patients and controls. Lifetime risk of elevated intraocular pressure was 42.5% in relatives of patients compared with 6.7% in relatives of controls (risk ratio = 6.3, 95% CI = 2.1-19.2; P < .001, log-rank test). Lifetime risk of enlarged cup-disc ratio was 62.2% in relatives of patients with glaucoma compared with 16.6% in relatives of controls (risk ratio = 3.8, 95% CI = 2.3-6.1; P = .001, log-rank test). Figure 3 shows the Kaplan-Meier lifetime risks of glaucoma. The lifetime absolute risk of glaucoma at age 80 years was 22.0% for relatives of patients compared with 2.4% for relatives of controls (risk ratio = 9.2, 95% CI = 1.2-73.9; P < .001, log-rank test).

The attributable proportion was calculated using the ratio of the lifetime cumulative risks of glaucoma in relatives as the best approximation of the true relative risk for genetic factors (relative risk = 9.2) in the Ape and App
was the earliest feature of glaucoma in relatives. Glaucoma is a disease that develops slowly. In most patients, it manifests in middle age and thereafter, and this age-dependent expression should be accounted for. Survival analysis is the method of choice for estimating the genetic risk in familial aggregation studies.28,30 From an epidemiological viewpoint, age at examination can be considered as adult-onset glaucoma. Generally, data from many ophthalmologists were used, which may have introduced nonstandardized diagnoses. Advantages of our study were as follows: (1) we ascertained patients with glaucoma and controls from the same population-based cohort, minimizing selection bias; (2) we did not rely on history data but actually examined all first-degree relatives; (3) we assessed each feature of glaucoma separately in a masked fashion to ensure an unbiased diagnosis; and (4) we aimed at full ascertainment and approached all patients with glaucoma in our source population. Ascertainment of probands and relatives was high and was similar among groups. A limitation of our study was the low number of patients, which decreased the statistical power of our study and created wide confidence intervals. However, the strength of the risk associations were strong enough to yield statistical significance. Glaucoma is a disease that develops slowly. In most patients, it manifests in middle age and thereafter, and this age-dependent expression should be accounted for. Survival analysis is the method of choice for estimating the genetic risk in familial aggregation studies.28,30 From an epidemiological viewpoint, age at examination can be

formulas (see the “Statistical Analysis” subsection in the “Participants and Methods” section). The attributable proportion among the genetically exposed (Ape) was 89%, indicating that 89% of the familial occurrence is genetically determined. The proportion of exposed patients (Pe) was calculated as the ratio of patient probands with affected relatives (n = 7) divided by the total number of patient probands (n = 38) with relatives who were at least 44 years old (minimum age of participants with glaucoma in our study). The attributable proportion of genetic factors to the overall occurrence of glaucoma in the general population (App) was 16.4%.

The main finding of this study is that the prevalences of glaucoma, enlarged cup-disc ratio, and elevated intraocular pressure are much higher in siblings and offspring of patients with glaucoma than in relatives of controls. The lifetime risk of glaucoma was 22% in relatives of patients with glaucoma, almost 10 times higher than that in controls. Our findings suggest that at least one sixth of all glaucoma in the general population may be caused by a genetic component. Enlarged cup-disc ratio was the earliest feature of glaucoma in relatives.

STATISTICAL ANALYSIS

The prevalence of glaucoma was compared between relatives of patients and controls. Prevalence figures were adjusted for age and sex. Multiple logistic regression analysis was used to estimate the prevalence odds ratio of glaucoma for relatives of patients, with relatives of controls as the reference group. Odds ratios were adjusted for age and sex and for the presence of diabetes mellitus and hypertension. Interaction between genetic factors and diabetes and hypertension was studied by performing stratified analyses and by performing analyses on the full data set, including product terms for diabetes and proband status (patient or control) and hypertension and proband status.

Survival analyses (Kaplan-Meier product-limit survival analyses) were performed to estimate cumulative lifetime risks of glaucoma, elevated intraocular pressure, and enlarged cup-disc ratio. Participants older than 80 years were pooled to maintain unbiased estimates.28 The log-rank test was used to compare survival curves of relatives of patients and relatives of controls. All analyses were performed with a statistical software package (BMDP Statistical Software Inc, Los Angeles, Calif).

The attributable proportion of genetic factors to the occurrence of glaucoma in the exposed and the general population was estimated using the formulas developed by Miettinen.29 The attributable proportion for the genetically exposed (Ape) was calculated with the formula Ape = (RR − 1) / RR, where RR is the relative risk. The attributable proportion for the total population (App) was calculated with the formula App = Ape × Pe, where Pe is the proportion genetically exposed among patients.

Previous family studies were limited to clinic-based families or to disorders that are nowadays not regarded as adult-onset glaucoma. Generally, data from many ophthalmologists were used, which may have introduced nonstandardized diagnoses. Advantages of our study were as follows: (1) we ascertained patients with glaucoma and controls from the same population-based cohort, minimizing selection bias; (2) we did not rely on history data but actually examined all first-degree relatives; (3) we assessed each feature of glaucoma separately in a masked fashion to ensure an unbiased diagnosis; and (4) we aimed at full ascertainment and approached all patients with glaucoma in our source population. Ascertainment of probands and relatives was high and was similar among groups. A limitation of our study was the low number of patients, which decreased the statistical power of our study and created wide confidence intervals. However, the strength of the risk associations were strong enough to yield statistical significance.

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other risk factors

Diabetes mellitus is a known risk factor for glaucoma.26 Also, a relationship between elevated intraocular pressure and hypertension has been shown previously.27 To investigate whether diabetes mellitus or hypertension could account for familial aggregation of glaucoma, both disorders were included in the analyses. Diabetes mellitus was defined by the use of antidiabetic medication, which was assessed using a questionnaire. Hypertension was defined by a systolic blood pressure of 160 mm Hg or higher, a diastolic blood pressure of 95 mm Hg or higher, or the use of drugs to lower blood pressure.

The main finding of this study is that the prevalences of glaucoma, enlarged cup-disc ratio, and elevated intraocular pressure are much higher in siblings and offspring of patients with glaucoma than in relatives of controls. The lifetime risk of glaucoma was 22% in relatives of patients with glaucoma, almost 10 times higher than that in controls. Our findings suggest that at least one sixth of all glaucoma in the general population may be caused by a genetic component. Enlarged cup-disc ratio was the earliest feature of glaucoma in relatives.

COMMENT

Enlarged cup-disc ratio, was used in our study. Participants with a cup-disc ratio of 0.7 or higher in at least 1 eye or asymmetry in cup-disc ratio of 0.3 or higher between both eyes were considered to have an enlarged cup-disc ratio.

All visual field charts were graded in a masked way by 2 independent graders using all available data calculated by the statistical software of the perimeter to eliminate visual field defects caused by media opacities.23-25 The graders were unaware of all clinical characteristics, including the cup-disc ratio, intraocular pressure, and familial relationship. Possible glaucomatous visual field defects were defined as defects not explainable by other abnormalities, such as retinal (eg, chorioretinal scars, macular degeneration, and vascular obstructions), optic disc (eg, optic disc drusen, optic disc pit, and tilted disc), or neurologic (eg, cerebrovascular accidents) disorders. Unreliable visual field test results were not included in the analyses. Consensus was reached if the graders differed in the grading of visual fields of probands and relatives.

The diagnosis of glaucoma was based on the presence of a glaucomatous visual field defect in combination with a cup-disc ratio of 0.7 or higher in the affected eye or an asymmetry in cup-disc ratio of 0.3 or higher between both eyes.

The attributable proportion for the total population (App) was calculated as the ratio of patient probands with affected relatives (n = 7) divided by the total number of patient probands (n = 38) with relatives who were at least 44 years old (minimum age of participants with glaucoma in our study). The attributable proportion of genetic factors to the overall occurrence of glaucoma in the general population (App) was 16.4%.

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Table 1. General Characteristics*

<table>
<thead>
<tr>
<th></th>
<th>Siblings (n = 67)</th>
<th>Of Controls (n = 142)</th>
<th>Offspring (n = 88)</th>
<th>Of Controls (n = 200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SE, y</td>
<td>72.3 ± 1.1†</td>
<td>75.4 ± 0.8</td>
<td>42.2 ± 0.9†</td>
<td>48.7 ± 0.6</td>
</tr>
<tr>
<td>Age range, y</td>
<td>54-96</td>
<td>45-94</td>
<td>25-81</td>
<td>23-73</td>
</tr>
<tr>
<td>Women, %</td>
<td>52.8</td>
<td>57.9</td>
<td>43.8</td>
<td>45.7</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>38.0</td>
<td>34.4</td>
<td>7.3</td>
<td>7.9</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>11.9†</td>
<td>3.8</td>
<td>1.2</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Values are mean ± SE or proportions adjusted for age and sex. †P < .05 for the difference with relatives of controls.

Table 2. Prevalence of Glaucoma Characteristics*

<table>
<thead>
<tr>
<th></th>
<th>Siblings</th>
<th>Of Controls</th>
<th>Offspring</th>
<th>Of Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean intraocular pressure, mm Hg</td>
<td>14.7 (0.4)†</td>
<td>13.1 (0.3)</td>
<td>14.7 (0.3)†</td>
<td>13.6 (0.2)</td>
</tr>
<tr>
<td>Intraocular pressure &gt;21 mm Hg, %‡</td>
<td>4.1 (1.9)</td>
<td>0.7 (1.2)</td>
<td>1.3 (1.0)</td>
<td>0.3 (0.6)</td>
</tr>
<tr>
<td>Intraocular pressure–lowering therapy, %</td>
<td>15.0 (2.9)†</td>
<td>1.4 (2.0)</td>
<td>0.0 (0.0)</td>
<td>1.5 (0.7)</td>
</tr>
<tr>
<td>Mean cup-disc ratio</td>
<td>0.54 (0.02)†</td>
<td>0.46 (0.01)</td>
<td>0.52 (0.01)</td>
<td>0.49 (0.01)</td>
</tr>
<tr>
<td>Cup-disc ratio &gt;0.7 or asymmetry &gt;0.3, %</td>
<td>32.8 (4.5)†</td>
<td>6.5 (3.0)</td>
<td>11.9 (3.4)</td>
<td>9.2 (2.2)</td>
</tr>
<tr>
<td>Visual field defect, %§</td>
<td>33.7 (4.8)†</td>
<td>10.8 (3.4)</td>
<td>3.6 (1.3)†</td>
<td>0.5 (0.9)</td>
</tr>
<tr>
<td>Prevalence of glaucoma, %|</td>
<td>10.4 (2.5)†</td>
<td>0.7 (1.7)</td>
<td>1.1 (0.7)</td>
<td>0.0 (0.0)</td>
</tr>
</tbody>
</table>

*All figures are, if appropriate, adjusted for age and sex. Values in parentheses are SEMs. †Statistically significant difference (P < .05) with relatives of controls. ‡Participants undergoing intraocular pressure–lowering therapy were excluded. §All visual field defects caused by retinal abnormalities, optic disc abnormalities (except glaucoma), or neurologic disorders were excluded. \Glaucoma was defined as the presence of a visual field defect (see the “Measurements” in the “Participants and Methods” section) in combination with a cup-disc ratio >0.7 or asymmetry in cup-disc ratio >0.3.

Table 3. Odds Ratios of Glaucoma Features for First-Degree Relatives*

<table>
<thead>
<tr>
<th></th>
<th>Present</th>
<th>Absent</th>
<th>OR (95% CI)§</th>
<th>OR (95% CI)§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siblings of patients</td>
<td>19</td>
<td>40</td>
<td>4.8 (2.1-11.1)</td>
<td>5.1 (2.2-12.2)</td>
</tr>
<tr>
<td>Siblings of controls</td>
<td>14</td>
<td>107</td>
<td>1.0 (0.1-9.7)</td>
<td>1.0 (0.1-9.7)</td>
</tr>
<tr>
<td>Offspring of patients</td>
<td>3</td>
<td>82</td>
<td>7.5 (0.7-76.9)</td>
<td>7.5 (0.7-76.5)</td>
</tr>
<tr>
<td>Offspring of controls</td>
<td>4</td>
<td>188</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The relative risks of family members in the control group are set to 1.0. OR indicates odds ratio; CI, confidence interval; and ellipses, not calculated. †All visual field defects caused by retinal abnormalities, optic disc abnormalities (except glaucoma), or neurologic disorders were excluded. ‡Glaucoma was defined as a visual field defect (see the “Measurements” subsection in the “Participants and Methods” section) in combination with a cup-disc ratio >0.7 or asymmetry in cup-disc ratio >0.3. §Adjusted for age and sex.

Table 4. Odds Ratios of Glaucoma Features for First-Degree Relatives*

<table>
<thead>
<tr>
<th></th>
<th>Present</th>
<th>Absent</th>
<th>OR (95% CI)§</th>
<th>OR (95% CI)§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraocular pressure &gt;21 mm Hg†</td>
<td>11</td>
<td>48</td>
<td>10.5 (2.7-41.0)</td>
<td>9.8 (2.5-38.9)</td>
</tr>
<tr>
<td>Siblings of patients</td>
<td>3</td>
<td>121</td>
<td>8.6 (3.4-21.9)</td>
<td>9.2 (3.5-24.1)</td>
</tr>
<tr>
<td>Siblings of controls</td>
<td>1</td>
<td>81</td>
<td>1.3 (0.5-3.1)</td>
<td>1.3 (0.5-3.1)</td>
</tr>
<tr>
<td>Offspring of patients</td>
<td>4</td>
<td>187</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The relative risks of family members in the control group are set to 1.0. OR indicates odds ratio; CI, confidence interval; and ellipses, not calculated. †Or intraocular pressure–lowering treatment. ‡Adjusted for age and sex. §Adjusted for age, sex, and the presence of hypertension or diabetes mellitus.
regarded as duration of exposure to genetic factors. So, conceptually, this aggregation study can be considered to be a longitudinal study, with age at examination as follow-up time. Adjustment for age-dependent expression is accomplished by censoring, and the true absolute lifetime risk for relatives is approximated.28 For simple genetic disorders, an absolute risk of 50% is compatible with autosomal-dominant inheritance, and an absolute risk of 25% is compatible with autosomal-recessive inheri-
tance.28 For complex disorders such as glaucoma, the interpretation of these proportions for mode of inheritance is not as straightforward. Moreover, it is likely that heterogeneity in familial risk is present. Different genes may be involved, each with their own mode of inheritance and interaction with environmental factors.

In relatives of patients with glaucoma, we found more diabetes, a known risk factor for glaucoma. However, the strength of the associations did not significantly alter after adjustment for diabetes mellitus. Diagnosis of diabetes was based on use of medication and not on fasting blood glucose levels. Untreated diabetes may, therefore, have been missed in relatives of patients and controls.

In general, the magnitude of any exposure in the cause of disease may be quantified by its relative and attributable risks. We found a relative risk of 9.2 for genetic factors, which is higher than the effect of any other known risk factor. In contrast, the population-attributable risk was approximately 16%, which was low. This suggests that other, nongenetic, factors determine the overall occurrence of glaucoma to a great extent.

We assessed intraocular pressure, cup-disc ratio, and visual field defects as independent manifestations of glaucoma. All 3 differed markedly between relatives of patients and controls. The difference was most prominent for enlarged cup-disc ratio. Even in the “normal” cup-disc range, the ratio was on average higher in relatives of patients. In addition, enlarged cup-disc ratio was the earliest manifestation of increased familial risk (Figures 1 and 2). Elevated intraocular pressure or use of therapy to lower intraocular pressure was more frequent in relatives of patients. Yet, most relatives who had been newly diagnosed as having glaucoma had normal intraocular pressures. The high prevalence of glaucoma therapy among relatives of patients may be a result of the selec-
tive treatment by ophthalmologists of patients with a positive family history.

In summary, we demonstrated that relatives of patients with glaucoma are at 10 times increased risk of developing glaucoma. Enlarged cup-disc ratio, not intraocular pressure, was the earliest expression of genetic exposure. Whether this familial aggregation is caused by genetic factors only or also by environmental factors needs further exploration.

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REFERENCES