Migraine and Vasospasm in Glaucoma: Age-Related Evaluation of 2027 Patients With Glaucoma or Ocular Hypertension

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Glaucoma is a multifactorial condition characterized by a progressive optic neuropathy and distinctive visual field loss. Normal tension glaucoma (NTG) differs from all other glaucomas, as it is the only condition with intraocular pressure (IOP) within the normal range of the population (10–20 mm Hg). This suggests that other risks factors apart from elevated IOP might play a particular role in NTG. Therefore, NTG is especially suitable to study IOP-independent risk factors. As in most complex diseases, the exact number of genes associated with the different glaucomas, their individual pathogenic contribution, and their specific ways of interaction with environmental susceptibilities remain largely unknown.1,2 For NTG, a robust association has been found with CDKN2BAS variants.3 The further identification of risk factors that offer potential targets for treatment options is of particular importance.

There is a female preponderance in NTG.4,5 Therefore, it is of interest which potential risk factors for glaucoma are more frequent in NTG than in other types of glaucoma and in females compared to males. Ischemia due to periodic vasoconstriction is considered as a potential risk factor for glaucomatous visual field damage,6–8 making both migraine and vasospasm potential risk factors for glaucoma. The aim of this study was to prospectively evaluate (1) the frequency of migraine, vasospasm, family history of migraine, and family history of glaucoma in patients with different types of glaucoma and ocular hypertension (OH), and also, the frequency of migraine and vasospasm in female and male patients, and the association of migraine and vasospasm in patients with glaucoma or OH; (2) whether migraine and vasospasm are more frequent in patients with family history of glaucoma than in patients without family history of glaucoma; (3) whether there is any difference in the frequency of migraine or vasospasm in different types of glaucoma compared to NTG; (4) the age-related frequency of migraine and vasospasm in NTG and primary open-angle glaucoma (POAG); and finally, (5) the frequency of migraine and vasospasm in relation to stage of visual field loss at diagnosis in patients with POAG and NTG.

Patients and Methods
By means of a detailed questionnaire,9,10 2170 glaucoma patients interviewed their siblings, children, parents, and...
relatives of mother and father (grandmothers, grandfathers, uncles, aunts) with 16 standardized questions. This resulted in information on family history of glaucoma in 12 groups of relatives for every patient. Results on family history of glaucoma and time of diagnosis from this cohort have been previously published.9 Details concerning the questionnaire and interview procedure have been previously described by the authors.10 The questionnaire used was designed for this study by the authors, as no such instrument was yet available. The original questionnaire (in German) has been published.9 Patients were consecutively recruited at the glaucoma service of the University Eye Hospital Wuerzburg. All glaucoma patients coming to the glaucoma service and seen by EG during the time of the study were asked for participation.

The first part of the questionnaire was always completed by the same glaucoma specialist (EG) at the patient’s visit, concerning type of glaucoma, age of the patient at diagnosis, and, for both eyes, the stage of visual field loss at diagnosis and maximal IOP, defined as the highest IOP ever measured. Concerning age at diagnosis, all patients were asked by the same glaucoma specialist at what age glaucoma had been diagnosed. This was verified from the medical records. If the answer was uncertain, the patient’s ophthalmologist was contacted by telephone while the patient was still in the examination room. Thus, age at diagnosis was evaluated in a uniform way and, if necessary, confirmed from multiple sources. Many of the patients included had been under the care of the same glaucoma specialist (EG) for more than 30 years. This ensured a high reliability of diagnosis, especially in NTG.

For staging of visual field loss, the first available and reliable visual field was chosen to judge glaucomatous visual field loss at or close to the time of diagnosis. Goldmann perimetry and in addition, wherever feasible, computerized threshold determining perimetry of the central visual field had been performed at diagnosis with, for example, Octopus perimeter 201 or Octopus perimeter 500 (program 32 and/or 31, or G1; Interzeag, Schlieren, Switzerland), Humphrey perimeter (program 30-1 and/or 30-2; Zeiss, Jena, Germany), or Competer (Taberna Pro Medicum, Lueneburg, Germany). Due to the change in perimetric equipment over the past decades, for the study the glaucoma specialist staged visual fields at diagnosis in both eyes according to the classification of Aulhorn.11 This ensured comparability between all perimetric results based on a descriptive staging method. The eye with more severe visual field loss was used for statistical evaluation. According to stage of visual field loss, patients were divided into two groups: with no or with beginning visual field loss (stages 0–II classification of Aulhorn) or with moderate to severe visual field loss (stages III–V).

The second part of the questionnaire contained the questions for the interviews of patients’ relatives on history of glaucoma or OH. Patients received instructions in a uniform way by the same glaucoma specialist (EG) at the patient’s visit, before using the questionnaire. The patients took the questionnaire home to perform the interviews of their relatives before returning the questionnaires. This was done for all patients in a uniform way by the same ophthalmologist (EG) reading out the questions on the questionnaire. Patients were asked for an established diagnosis of migraine and about migraine headache characteristics according to the criteria of the International Headache Society.12 Concerning vasospasm, patients were asked whether they suffered from “sudden episodes of cold and pale fingers.” A positive/negative answer signified presence/absence of vasospasm. For all patients reporting vasospastic symptoms, oral therapy with magnesium was advised, as this treatment has been recommended by several experts.6–13 However, patients were informed about the lack of final evidence for benefit of magnesium therapy in this context from controlled studies, and the possibility that costs for this therapy might not be covered by insurance. They were informed about the expert opinions. Additional information on migraine and vasospasm was derived from patients’ medical records. Patients reporting migraine symptoms in recent years were additionally referred to a neurologist for neurologic evaluation and therapeutic recommendations.

The study adhered to the tenets of the Declaration of Helsinki and written informed consent from participants was obtained.

We received 2170 questionnaires suitable for evaluation. Details on demographic and ophthalmologic data for these patients are shown in Table 1. Of 2027 patients who provided a “yes” or “no” answer on migraine diagnosis, 1244 had POAG, 140 NTG, 49 pigmentary glaucoma (PG), 64 pseudoxfoliation glaucoma (PEX), 138 OH, and 218 primary angle closure glaucoma (PACG). One hundred seventy-four patients had other types of glaucoma, which are not evaluated here due to small sample sizes and are published separately.14–16 A total of 2015 patients provided a “yes” or “no” answer regarding diagnosis of vasospasm.

In our study NTG was defined as glaucomatous optic neuropathy and visual field loss with maximal IOP up to diagnosis not exceeding 21 mm Hg. A small number of NTG patients had pressure spikes > 21 mm Hg in single measurements and these patients were therefore admitted for inpatient IOP monitoring including measurements at night. If the pressure spike could not be confirmed by repeated diurnal tension curves, patients remained in the diagnosis group of NTG. All patients with NTG received IOP-lowering therapy.

Fisher’s exact test 2-sided, Mantel-Haenszel z2 test, Cochran–Armitage trend test, and Cochran-Mantel-Haenszel statistics based on table scores were used for statistics. Due to the explorative nature of the analysis no adjustment of α error was performed. A P value ≤0.05 was considered statistically significant.

**RESULTS**

**Frequency of Migraine and Vasospasm in Patients With Glaucoma**

Of 2027 patients who answered the question on migraine, 13.7% (277) reported episodes of migraine. Family history of migraine was established in 30.8% of all patients answering the
question on family history of migraine (347 of 1127 patients). Vasospasm was reported by 19.0% of patients (385 of 1557). Migraine and vasospasm were significantly more frequent in females with 18.1% (203 of 1120 female patients providing information on migraine) and 20.7% (232 of 1119 female patients providing information on vasospasm), respectively, than in males with 8.2% (70 of 859 male patients providing information on migraine; 84 of 366 patients with vasospasm who provided a yes answer on migraine), compared to 20.7% (232 of 1119 female patients providing information on vasospasm), respectively.

Association of Migraine and Vasospasm in Patients With Glaucoma or OH

Twenty-three percent of patients with vasospasm also suffered from migraine (84 of 366 patients who provided a “yes” or “no” answer on migraine), compared to 11.7% of patients without vasospasm (186 of 1586 patients without vasospasm who provided a “yes” or “no” answer on migraine). Thus, glaucoma patients with vasospasm had a 2-fold higher frequency of migraine than patients without vasospasm ($P < 0.0001$, Mantel-Haenszel $\chi^2$ test) and 16.7% (142 of 850 male patients providing information on vasospasm; $P = 0.02$, Mantel-Haenszel $\chi^2$ test), respectively.

Frequency of Migraine and Vasospasm in Patients With and Without Family History of Glaucoma

Of 2027 patients who answered the question on migraine, 40.3% (817) reported a family history of glaucoma. Details on family history of glaucoma in different glaucomas from this cohort have been reported previously. Patients with family history of glaucoma had a significantly higher frequency of migraine (129 of 817; 15.8%) than patients without family history of glaucoma (148 of 1210; 12.2%; Fisher’s exact test 2-sided, $P = 0.02$). There was no significant difference in the frequency of vasospasm between patients with family history of glaucoma (154 of 810; 19.0%) and without family history of glaucoma (229 of 1205; 19.0%; Fisher’s exact test 2-sided, $P = 1.0$).

Of all patients, 1799 reported having siblings. Nine patients did not answer this question. The total number of sisters was 2420, and the number of sisters still alive at the time of the study was 1938. In 235 of these sisters, glaucoma or OH had been diagnosed. The total number of brothers was 2560, and the number of brothers still alive at the time of the study was 1565. In 158 of these brothers, glaucoma or OH had been diagnosed.

### Frequency of Migraine in Different Types of Glaucoma Compared to Frequency of Migraine in NTG

The frequency of migraine in patients with POAG was 13.1%, with NTG 21.4%, PG 24.5%, OH 13.8%, PEX 7.8%, and PACG 10.1% (see Table 2). There was a significant difference in migraine frequency between POAG and NTG ($P = 0.01$, Fisher’s exact test, 2-sided), between PEX and NTG ($P = 0.02$), and between PACG and NTG ($P = 0.004$). There was no significant difference in migraine frequency between OH and NTG ($P = 0.1$), and between PG and NTG ($P = 0.7$). The probability of a patient with NTG to have migraine was increased by 63.5% compared to a patient with POAG when correcting for age ($P = 0.007$, Cochran-Mantel-Haenszel statistics based on table scores). This equals a relative risk of

<table>
<thead>
<tr>
<th>Type of Glaucoma</th>
<th>Patients With Migraine</th>
<th>Fisher’s Exact-Test (2-Sided), $P$</th>
<th>Patients With Vasospasm</th>
<th>Fisher’s Exact-Test (2-Sided), $P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTG</td>
<td>30 of 140</td>
<td>21.4</td>
<td>31 of 156</td>
<td>22.8</td>
</tr>
<tr>
<td>POAG</td>
<td>163 of 1244</td>
<td>13.1</td>
<td>227 of 1241</td>
<td>18.3</td>
</tr>
<tr>
<td>PEX</td>
<td>5 of 64</td>
<td>7.8</td>
<td>17 of 62</td>
<td>27.4</td>
</tr>
<tr>
<td>OH</td>
<td>19 of 138</td>
<td>13.8</td>
<td>22 of 158</td>
<td>15.9</td>
</tr>
<tr>
<td>PACG</td>
<td>22 of 218</td>
<td>10.1</td>
<td>40 of 220</td>
<td>18.2</td>
</tr>
<tr>
<td>PG</td>
<td>12 of 49</td>
<td>24.5</td>
<td>8 of 50</td>
<td>16.0</td>
</tr>
</tbody>
</table>

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<th>Patients With Vasospasm</th>
<th>Fisher’s Exact-Test (2-Sided), $P$</th>
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<td>27.4</td>
</tr>
<tr>
<td>OH</td>
<td>22 of 158</td>
<td>15.9</td>
</tr>
<tr>
<td>PACG</td>
<td>40 of 220</td>
<td>18.2</td>
</tr>
<tr>
<td>PG</td>
<td>8 of 50</td>
<td>16.0</td>
</tr>
</tbody>
</table>
The frequency of migraine in patients with NTG and POAG in five age groups. Frequency of migraine in NTG for age group < 41 years was 50% (4 of 8 patients); 41 to 50 years, 42.9% (6 of 14 patients); 51 to 60 years, 30.8% (8 of 26 patients); 61 to 70 years, 17.1% (7 of 41 patients); and 71 to 80 years, 8.0% (2 of 25 patients). Frequency of migraine in POAG for age group < 41 years was 23.1% (12 of 52 patients); 41 to 50 years, 20.8% (25 of 120 patients); 51 to 60 years, 20.8% (51 of 245 patients); 61 to 70 years, 11.0% (47 of 428 patients); and 71 to 80 years, 7.9% (21 of 265 patients).

Frequency of Migraine and Vasospasm in Glaucoma

The frequency of migraine, assessed for the total patient cohort, decreased significantly with age in both NTG and POAG (Cochran-Armitage trend test, \( P < 0.0001 \)). This age effect was significant in male (Cochran-Armitage trend test, \( P < 0.0001 \)) but not in female (Cochran-Armitage trend test, \( P = 0.02 \)).

Age-Related Frequency of Migraine

The frequency of migraine, assessed for the total patient cohort, decreased significantly with age (age < 30 years, 31.0%; 31–40 years, 27.5%; 41–50 years, 23.4%; 51–60 years, 20.8%; 61–70 years, 10.7%; 71–80 years, 8.1%; Cochran-Armitage trend test, \( P < 0.0001 \)). This was found for male (Cochran-Armitage trend test, \( P < 0.0001 \)) as well as female (Cochran-Armitage trend test, \( P < 0.0001 \)).

Age-Related Frequency of Vasospasm

The frequency of vasospasm, assessed for the total patient cohort, decreased significantly with age (age < 30 years, 34.5%; 31–40 years, 21.6%; 41–50 years, 20.0%; 51–60 years, 21.5%; 61–70 years, 15.5%; 71–80 years 17.8%; Cochran-Armitage trend test, \( P = 0.01 \)). This age effect was significant in female (Cochran-Armitage trend test, \( P = 0.02 \)) but not in male patients (Cochran-Armitage trend test, \( P = 0.3 \)).
70 to 79 years, which was marginally stronger in glaucomas with elevated IOP. Cursiefen and colleagues have found that migraine is significantly more frequent in patients with NTG than in high-pressure glaucoma or control subjects. A population-based study has found no difference in the prevalence of open-angle glaucoma in patients with or without migraine. However, the low number of patients with NTG in this study does not allow for a definite conclusion on an association between NTG and migraine.

The frequency of glaucoma increases and that of migraine decreases with age. In our study, the age-corrected evaluation showed that patients with NTG had a 63.5% higher probability, with a 1.6-times higher relative risk, of suffering migraine than patients with POAG. This is a relevant finding concerning pathophysiology of NTG, as migraine-associated changes in blood flow are a more frequent risk factor in NTG. Although the exact pathophysiology of migraine has not yet been clarified, migraine is currently considered to be a neurovascular syndrome caused by activation of nociceptors innervating the meningeal blood vessels. It has been demonstrated that choroidal thickness increases significantly during acute migraine attacks. Dadaci and colleagues have hypothesized that this might be the expression of neurogenic inflammation in the eye, evidence for disturbance of autonomic activity, and alteration of ocular circulation. Decreased blood flow in the ophthalmic arteries has been shown to be associated with glaucoma progression. Interestingly, there is a report about the reproducible cessation of migraine in a patient with NTG undergoing therapy with the prostaglandin analog latanoprost.

The significantly higher frequency of migraine in women is well established in population-based studies and was also found in our study population. The higher frequency of migraine in women might contribute to the higher frequency of females affected by NTG. In a previous study (Gramer E, IOVS 2006;47:ARVO E-Abstract 3395), we have found a strong female preponderance in NTG but could show that females are not affected more severely by visual field loss than males. The female preponderance in NTG has been previously described in several studies but so far cannot be well explained. Some authors have hypothesized that it could result from the higher proportion of females in elderly populations, and the fact that NTG is a disease of older people. In other parts of our study we could however show that NTG is not truly a "disease of the elderly" but rather a disorder that is often only diagnosed at a late stage of the disease, when visual field loss has progressed to a higher stage, and therefore also at a more advanced age, than other types of glaucoma.

### Table 3. Frequency of Migraine and Vasospasm in NTG and POAG Patients With Different Stages of Visual Field Loss

<table>
<thead>
<tr>
<th>Type of glaucoma</th>
<th>Patients, n</th>
<th>Patients With Migraine, n</th>
<th>Patients With Migraine in Stages 0–II of VFL</th>
<th>Patients With Migraine in Stages III–V of VFL</th>
<th>Fisher’s Exact Test 2-Sided, P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTG</td>
<td>130</td>
<td>31</td>
<td>16 of 76 = 21.1%</td>
<td>15 of 54 = 27.8%</td>
<td>4 of 240 = 16.1%</td>
</tr>
<tr>
<td>POAG</td>
<td>1219</td>
<td>220</td>
<td>16 of 79 = 21.1%</td>
<td>12 of 58 = 21.0%</td>
<td></td>
</tr>
<tr>
<td>NTG</td>
<td>134</td>
<td>28</td>
<td>16 of 79 = 21.1%</td>
<td>12 of 58 = 21.0%</td>
<td>0.6</td>
</tr>
<tr>
<td>POAG</td>
<td>1223</td>
<td>160</td>
<td>127 of 964 = 13.1%</td>
<td>55 of 259 = 21.1%</td>
<td></td>
</tr>
</tbody>
</table>

### Family History of Glaucoma and Migraine

To our knowledge this is the first study to evaluate family history of migraine in glaucoma patients and to assess the association of family history of glaucoma and frequency of migraine. We showed that glaucoma patients frequently report a family history of migraine, and that patients with family history of glaucoma had a significantly higher frequency of migraine than patients without family history of glaucoma. This might point to a common, possibly polygenetic etiology of these two diseases, which both reveal a familial component. The molecular mechanisms of migraine are still not well understood. Recently, several new susceptibility loci for migraine have been identified, many of them located in genes with known functions in synaptic or neuronal regulation. Suzuki and colleagues have found homozygous mutations in SLC4A4, encoding the Na⁺-HCO₃⁻ cotransporter NBCe1, in two sisters with ocular abnormalities and hemiplegic migraine. Several members of this pedigree heterozygous for the mutation presented with glaucoma and migraine. Previous studies have provided
evidence for an association with the endothelial nitric oxide synthase gene in patients with both glaucoma and migraine. These findings point to a genetic determination of vasospastic disorders in these patients, which could be of relevance for development of both migraine and glaucoma, for example, due to impaired vascular autoregulation.

A study on NTG has found an association of single nucleotide polymorphisms in the genes for Mitofusin 1 and 2, suggesting an involvement of mitochondrial inheritance and relevance of mitochondrial alterations in NTG. However, like for many other glaucoma genes, the association of Mitofusin 1 and 2 and NTG has so far not been replicated in other studies. Previous results from our study have shown a higher frequency of maternal history of glaucoma compared to paternal history in POAG, NTG, and OH. For NTG this finding has also been reported by other studies. This could support the involvement of mitochondrial dysfunction in glaucoma, as mitochondria are exclusively inherited from the mother.

Prognostic Factors

A prognostic factor is a factor that influences the course of a disease after its onset and may allow predictions about the progress of a disorder. This factor can be, but does not necessarily have to be, also a risk factor for the disease. Concerning the stage of visual field loss at diagnosis, we did not find evidence that migraine or vasospasm is a prognostic factor in POAG or NTG, as patients with a higher stage of visual field loss at diagnosis did not suffer from migraine or vasospasm more frequently than patients with beginning visual field loss at diagnosis. However, our study did not include a follow-up of visual field progression in individual patients with and without migraine or vasospasm, which would be necessary to fully elucidate the prognostic aspect. The Collaborative Normal-Tension Glaucoma Study found a higher risk for progression of visual field loss in NTG patients with migraine.

Vasospasm and Glaucoma

The prevalence of vasospasm of 19% in our patients, was in the described range for the general population (11%-19%). Drance and colleagues have found peripheral vasospastic reactions to cooling in 65% of patients with NTG not suffering from migraine. This frequency of vasospastic reactions is similar to that in nonglaucomatous patients with migraine and significantly higher than in a control group. In our study the frequency of vasospasm was higher in female patients but did not differ between different glaucomas. However, we found an association of migraine and vasospasm in our large cohort of glaucoma patients. The association of migraine and vasospasm has previously been demonstrated in a group of nonglaucomatous patients by measurement of blood cell velocity using nailfold videomicroscopy.

It has been reported that patients with vasospastic diseases also have a high prevalence of clinical features of connective tissue diseases. Other studies have found associations of migraine with Raynaud disease, and of migraine with connective tissue disorders. Genome-wide association studies for migraine have identified several susceptibility loci. Mutations in one of the potentially relevant genes, TGFBR2, have also been reported to cause monogenic Marfan’s syndrome. This reflects possible comorbidities between migraine, connective tissue diseases, and vascular disorders, which might all be relevant in the pathogenesis of glaucoma within the interaction of multifactorial ocular, systemic, and genetic risk factors, as illustrated in Figure 3.

Impaired autoregulation of blood flow in the optic nerve head can result from diminished perfusion pressure, increased blood viscosity, or increased vascular resistance. Thus, vasospasm, leading to impaired autoregulation of blood flow in the optic nerve head, is a potential risk factor for glaucoma. Recently, the combination of primary vascular dysregulation with a cluster of additional symptoms has been classified as “Flammer syndrome.” However, in our study we did not evaluate the additional symptoms of Flammer syndrome besides “sudden episodes of cold and pale fingers.” This would have complicated the already extensive questionnaire addressed mainly to elderly persons. Thus, our study does not allow any conclusions about the relationship between glaucoma and vasospastic syndrome, primary vascular dysregulation, or Flammer syndrome.
Concerning treatment, magnesium has been repeatedly recommended as a possible treatment option in primary vascular dysregulation. However, there is no final evidence for a beneficial effect from randomized controlled trials.\textsuperscript{6,13} It has been reported that magnesium leads to stabilization of visual field in glaucoma patients with vasospasm\textsuperscript{5,3} and that calcium antagonists also have a beneficial effect.\textsuperscript{3,4,5} Our hypothesis is that migraine, vasospasm, Raynaud disease, and NTG could be the expression—in individual combinations varying between patients—of a generalized vasospastic disorder (see Fig. 3).\textsuperscript{17} Morphologic alterations of the optic disc, which are more frequent in NTG,\textsuperscript{56} suggest a possible genetic disposition toward less connective tissue of the lamina cribrosa in NTG.

Migraine and vasospasm are important risk factors, because therapeutic options are available, in contrast to genetic risk factors, which might influence susceptibility for the disease.\textsuperscript{3,5,8,57}

**Strengths and Limitations of This Study**

One strength of this study was that assessment of family history of glaucoma and other risk factors was performed in different glaucomas in a uniform way, by one glaucoma specialist using the same methods. This approach allowed us to assess differences in risk factors between the glaucomas. No preselection of patients was performed, but all patients coming to the glaucoma clinic and seen by EG were asked consecutively for participation. The participation rate was very high, as most patients had been under the care of the glaucoma specialist (EG) for several decades. Only a small number of patients (approximately 10–15 patients) refused to participate in the study in the first place. Reported reasons for this were the fact that they had no living relatives, had been adopted, or there was uncertainty about paternity in the family. There was no charge for mailing the questionnaire, thus there was no financial reason not to return it. The number of unreturned questionnaires is unfortunately not available. However, the fact that the first and third part of the questionnaire were completed by the ophthalmologist at the time of the visit in the glaucoma clinic should have encouraged patients with and without migraine or vasospasm, and with and without family history of glaucoma, equally to complete and return the questionnaire. Patients had been informed that the additional information on family history from the study would also be used to complete their medical record and would therefore also be available in future patient care. This should have motivated patients with and without family history of glaucoma to return the questionnaire. Also, some questions concerned additional risk factors, such as low blood pressure, heart disease, or systemic medication, which again should have encouraged patients with and without migraine or vasospasm to complete and return the questionnaire.

The fact that all tasks were performed by only one glaucoma specialist is regarded as a particular strength of this study, allowing for high comparability between different glaucoma types. However, staging of the disease and questionnaire instructions by only one observer can theoretically also create a bias. Even if a selection, observer, or ascertainment bias of some extent cannot be excluded, this should equally affect all types of glaucoma, thus still allowing for comparison of, for example, frequency of migraine, vasospasm, and family history of glaucoma between the glaucoma types.

The diagnosis of migraine is currently based on patient history and there is no technical instrument to verify this diagnosis. Information on diagnosis of migraine or vasospasm was established by questioning of the patients in a uniform way by the same glaucoma expert and in addition confirmed from medical records of patients who had previously been evaluated by a neurologist. Patients with migraine symptoms in recent years were referred to a neurologist for evaluation and therapy. The diagnosis of vasospasm in this study was established by reported clinical symptoms and patients’ medical records only—objective measurements such as nailfold videomicroscopy\textsuperscript{15,46} could not be performed as part of this study focused on family history of glaucoma in a large patient cohort.

**Conclusions**

Migraine is significantly more frequent in NTG than in other types of glaucoma. Patients with NTG had a 63.5% higher probability, with a 1.6-fold higher relative risk, of having migraine than patients with POGM when correcting for age. There is no evidence from our study that migraine or vasospasm is a prognostic factor regarding the extent of visual field loss in glaucoma at diagnosis. The higher frequency of migraine and vasospasm in females as found in our study could contribute to the female preponderance in NTG. Treatment of the potential risk factors migraine and vasospasm should be performed in all types of glaucoma. Patients with family history of glaucoma have a significantly higher frequency of migraine than patients without family history of glaucoma. Our findings suggest an association of NTG and migraine and a common, possibly polygenic, vascular etiology of these two diseases with familial predisposition.

**Acknowledgments**

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**References**


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