FAMILIAL TRENDS IN A POPULATION WITH MACULAR HOLES

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Purpose: To determine if patients with macular hole report an increased family history of macular hole compared with control patients and compare the report of family history between patients with unilateral and bilateral macular holes.

Methods: This was a multicenter case–control study. Charts of patients coded with diagnosis of macular hole were reviewed, and the diagnosis of idiopathic full-thickness macular hole was ascertained in 166 patients. The control group comprised 136 patients without macular hole or trauma who presented with senile cataract. Family history was obtained from all patients through a telephone interview.

Results: Six of 166 (3.6%) macular hole patients surveyed reported a history of macular hole in a primary relative compared with none of 136 (0.0%) control patients (odds ratio is infinity, with 95% confidence interval 1.295 to infinity); however, this finding may be explained by confounders such as age and number of family members. Two of the 142 (1.4%) patients with unilateral holes versus 4 of the 24 (16.7%) patients with bilateral holes reported a family history (odds ratio is 0.0714, with 95% confidence interval 0.0063 to 0.5537), and this finding remains significant when logistic regression is performed to evaluate variables of age and number of family members as potential confounders.

Conclusion: There is an increased report of familial occurrence of macular hole in patients with macular holes compared with control patients; however, logistic regression relates this finding to variables of age and number of family members. Patients with bilateral macular holes are more likely to report a family history of macular hole than patients with unilateral macular holes, and this finding remains significant in the presence of age and number of family members. These findings may suggest a familial component to macular hole.

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Idiopathic macular hole has a prevalence of 3.3 per 1000 in people aged >55 years and primarily affects women.[1] Idiopathic macular hole was first described in 1869 by Knapp[2] and later by Noyes.[3] Since a surgical treatment was described for this condition in 1991, there has been renewed interest in the pathophysiology and natural history of macular holes.[4] Refinements in the surgical technique, and a better understanding of the predictors for visual outcome, have led to greater success in pars plana vitrectomy for treatment of macular hole.[5] In addition, a recent study has shown that small macular holes can be successfully treated nonsurgically with intravitreal microplasmin.[6]

The pathophysiology of macular hole was described initially by Dr. Gass and has been further elucidated by optical coherence tomography.[7] Idiopathic macular holes form in some patients with pathologic vitreofoveal attachment when they develop age-related contraction of the posterior hyaloid. Surgical closure of a macular hole involves a vitrectomy to relieve the vitreofoveal traction and intravitreal gas to tamponade the macular hole. Internal limiting membrane peeling may increase the rate of macular hole closure after vitrectomy and gas–fluid exchange.[8]

A familial component to some cases of idiopathic macular holes was suggested by one study describing

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four families each of which had multiple family members afflicted with macular holes. The authors proposed a genetic component to the disease.[9]

To further investigate the existence of familial idiopathic macular holes, we performed a case–control study examining the report of a family history of macular hole in macular hole patients compared with that in a control population.

Methods

This retrospective case–control study was approved by the Institutional Review Board of the University of South Florida. It was conducted at the University of South Florida and a private retina practice in Clearwater, FL. Electronic records over a recent 5-year period were searched for a diagnosis of macular hole. The charts of patients with this diagnosis were reviewed to select those with idiopathic macular hole. Trauma-induced macular holes were excluded from the study as were pseudomacular holes and lamellar macular holes. Also, any patients with previous vitrectomy surgery, retinal detachment repair, or retinal vascular disease were excluded from the study. Control subjects for this study were gathered from a sequential list of patients who had undergone cataract surgery at the University of South Florida. Any macular hole patients were not considered for the control population. The medical records of all the control patients were reviewed to verify that no control patient had a macular hole.

Patients were surveyed by mail with subsequent telephone interview follow-up and asked if they had any primary family members with a macular hole (in parents, siblings, or children). An attempt was made to contact all family members to confirm report of macular hole history. In all family members alleged to have macular hole(s), ophthalmic medical records were reviewed if available for confirmation of macular hole diagnosis. Patients without macular hole were also surveyed to investigate the report of a family history of macular hole in a control population.

The primary exposure measure of this study was the report of a family history of macular hole in macular hole patients compared with control patients. A secondary measure of this study was the report of a family history of macular hole in patients with unilateral macular hole compared with that in patients with bilateral macular holes. Statistical analyses were performed using the SAS system Version 9.2 (SAS Institute, Inc, Cary, NC). Analyses include Fisher exact test, *t*-tests (on continuous variables), and logistic regression (for exploring potential confounders). Odds ratios, 95% confidence intervals (95% CI), and *P* values were reported.

Results

Survey questionnaires were sent to 190 patients with the diagnosis of idiopathic macular holes and 187 control patients. Sixty-six percent of the macular hole patients and 60% of the control patients were women. One hundred and sixty-six patients (87%) with macular holes and 136 (73%) control patients either completed the survey or participated in a follow-up telephone interview. The average age of the responding macular hole patients was 72.6 years with a standard deviation of 8.2. The average age of the responding control patients was 67.9 years with a standard deviation of 12.6. There was a statistically significant difference in age between the macular hole group and the control group ($P = 0.0003$). The average number of family members in the macular hole group was 5.8 with standard deviation of 2.9. In the control group, the average number was 4.9 with standard deviation of 3.8. There was a statistically significant difference in the number of family members between the macular hole group and the control group ($P = 0.02$). There was no statistically significant age difference between those who completed the survey ($P = 0.64$) and those who did not ($P = 0.24$), nor was there a significant difference in gender between those who completed the survey ($P = 0.45$) and those who did not ($P = 0.49$). Table 1 displays demographic information (age, gender, number of primary family members) for macular hole and control patients.

Table 1. Demographic Data Including Number of Patients Surveyed, Age of Patients, Gender, and Number Of Family Members

	Number Surveyed	Age (Median)	% Female Patients	Number of Family Members
Macular hole patients	166	72.6	66	5.8
Control patients	136	67.9	67	4.9

Table 2. Initial and Final Visual Acuities in Macular Hole Patients

Visual Acuity of Macular Hole Patients	Initial Visual Acuity	Final Visual Acuity
>20/40	4%	33%
20/40 to 20/80	31%	28.5%
20/80 to 20/200	48%	28.5%
<20/200	17%	10%
	Average: 0.854 logMAR (20/143)	Average: 0.654 logMAR (20/90)

Table 2 presents pertinent initial and final visual acuity information for macular hole patients. In all, 75.1% of macular hole patients underwent surgery for macular hole repair.

Six of 166 (3.6%) macular hole patients surveyed reported a history of macular hole in a primary relative compared with none of 136 (0.0%) control patients (the exact P value is 0.034 and odds ratio is infinity, with 95% confidence interval 1.295 to infinity). All six of the patients claiming a family history reported only one family member with a diagnosis of macular hole. We confirmed the diagnosis of idiopathic macular hole in these six family members through a telephone interview. In 5 of these 6 family members, we confirmed the diagnosis through a review of the patient's medical record. Logistic regression was performed to evaluate pertinent possible confounding variables. The finding of higher report of family history was explained by variables of age and number of family members (P = 0.001 for age, P = 0.0027 for number of family members, and P = 0.9851 for report of family history).

Of the 166 responding macular hole patients surveyed, 142 (85.5%) patients had unilateral macular holes and 24 (14.5%) had bilateral macular holes. Two of the 142 (2.1%) patients with unilateral holes versus 4 of the 24 (16.7%) patients with bilateral holes reported a family history (the exact P value is 0.0043 and the odds ratio is 0.0714, with 95% confidence interval 0.0063 to 0.5537). The average age in the unilateral macular hole group was 72.0 with standard deviation of 8.2 and that in the bilateral group was 75.7 with standard deviation of 8.0. There was only a marginally significant age difference between the unilateral macular hole group and the bilateral macular hole group (P = 0.05). The average number of family members in the unilateral macular hole group was 5.0 with standard deviation of 2.9. In the bilateral group, the average was 4.5 with standard deviation of 2.9. There was no statistically significant difference in number of family members between the unilateral macular hole group and the bilateral macular hole group (P = 0.4343). The association of higher report of family history remains significant when logistic regression is performed in the comparison of unilateral to bilateral macular holes (P = 0.0742 for age, P = 0.2286 for number of family members, and P = 0.0046 for family history).

Discussion

In our study, 3.6% of patients with idiopathic macular hole had a primary relative with an idiopathic macular hole. The 3.6% report of macular hole in family members of patients with macular hole is higher than the 0% report of macular hole found in the control group and higher than the 0.3% prevalence of macular hole in the general population reported in other studies,[1] although this finding may be explained by differences in age and number of family members as discussed more thoroughly below. Patients with bilateral macular holes had a statistically significant higher report of family history than the patients with unilateral macular holes, and this association was not lost after controlling for variables of age and number of family members by logistic regression. This familial trend in bilateral disease may suggest a genetic component to some macular holes. It is impossible at this point to say more pertaining to the attributable proportion of genetic predisposition versus environmental influence in pathogenesis of disease, until we perhaps find a genetic mutation in these individuals, and then can more meaningfully comment on the prevalence of that genetic variation in unaffected individuals. It is likely that macular holes are caused by an interplay between genetic predisposition and modifiable environmental risk factors.

With an increasing emphasis on genetics in current-day medicine, many diseases that have previously been referred to as ''idiopathic'' are now subject to reinvestigation. Interest in a possible genetic component of a disease or syndrome arises when a familial pattern is observed. In the case of age-related macular degeneration, genetic predisposition has been demonstrated by familial aggregation studies and twin studies.[10] Using genome linkage scan and association studies, multiple potentially causative genes have been identified.[11] As demonstrated with the Beaver Dam Eye Study, identifying sibling correlation in disease can be the first step in the search for genetic transmission.[12]

Bilaterality of a retinal disease also raises suspicion of a genetic and thereby familial component. Macular dystrophies such as Best vitelliform macular dystrophy

and adult-onset vitelliform macular dystrophy demonstrate this phenomenon of bilateral involvement in diseases with identified genetic mutations.[13,14] Retinitis pigmentosa is another example of bilateral symmetry of inherited retinal disease.[15] In our study, 14.5% of patients with macular holes had bilateral macular holes. The occurrence of bilaterality is slightly higher than in previous studies, which report between 7% and 12% of patients with macular holes with bilateral disease.[16,17] The bilaterality of many cases of macular holes suggests a possible genetic component to macular hole. The occurrence of bilaterality in our study is probably underestimated given the short 5-year follow-up of the study. However, our follow-up length of time is matched between macular hole patients to controls. Our primary end point was not to investigate the prevalence of bilateral macular holes, as this has been previously well described. We were primarily interested in the family history component, and the occurrence of bilaterality was something that we reported secondarily.

Interestingly, the report of a positive family history of macular hole was much higher in patients with bilateral macular hole (17%) than in patients with unilateral macular hole (1%). This finding that patients with bilateral macular hole are more likely to have a positive family history of macular hole than patients with unilateral macular holes might be useful in guiding future studies searching for cases of familial macular hole. The identification of cases of familial macular hole is useful in searching for a genetic component to this disorder. The strong association between family history and bilateral macular holes has clinical implications. The association between having bilateral disease and a positive family history suggests that unilateral macular hole patients with an affected family member should have close monitoring of their fellow eye if there is not a complete posterior vitreous detachment. Home Amsler grid testing and periodic optical coherence tomography scans of the unaffected eye may allow for early detection of a macular hole. Such detection may be important as there is evidence that earlier intervention with macular hole surgery may result in better anatomic and visual outcomes.[18] Further studies might even show a benefit of preemptive treatment with intravitreal microplasmin in the fellow eye of patients with macular hole who have a positive family history of macular hole.[6]

As originally suggested by Dr. Gass, the vitreoretinal interface is an area of interest in explaining macular hole formation, and this is likely a good starting point to target genetic screening of familial macular hole patients.[19] Optical coherence tomography suggests that idiopathic macular holes are caused by tractional forces associated with perifoveal vitreous detachment. A new stage of macular hole, ''Stage 0,'' based on optical coherence tomography observations of the vitreoretinal interface in fellow eyes of patients with unilateral idiopathic macular holes has been introduced in the literature.[20] Genes involved in collagen synthesis are prime targets for genetic studies on macular hole. A recent article investigating messenger RNA expression in retinectomy tissue has suggested that Type VI collagen could be involved in vitreoretinal attachment as collagens are important macromolecules that contribute to adhesion at the vitreoretinal interface.[21] Type II collagen and fibronectin have also been noted as possibly contributing to vitreoretinal adhesion.[6] It is possible that a mutation exists in one of the genes coding for a component of the vitreoretinal interface that might explain cases of familial macular holes. If a genetic association is identified in macular hole patients, it is likely to be a multifactorial rather than a single causative genetic factor.

There are several limitations to this study. First, although there appeared to be a statistically significant association with higher report of family history by macular holes patients compared with control patients, it must be recognized that the difference between 3.6% and 0% is not large, and in our study this finding appears to be confounded by variables of age and number of family members. Logistic regression was performed to determine if the association of higher report of family history between compared populations was present after adjustment for age or number of family members—and the association was lost when comparing macular hole patients with control patients. The absolute age range between the macular hole and control groups (72.6 years in macular hole patients and 67.9 years in control patients) was less than 5 years, so it is possible that this gap in age, albeit statistically different, is not clinically relevant for macular hole development risk. The finding of higher report of family history in the bilateral macular hole group compared with the unilateral macular hole group interestingly remained statistically significant even when the variables of age and number of family members were accounted for by logistic regression. Of note, the proximity in median age (<5 years) between the macular hole group and control group was not was intentional, as these patients were sequentially collected. The similarity in age probably reflects age as a shared risk factor for senile cataract and macular hole. All control patients were cataract surgery patients from the University of South Florida Ophthalmology Clinic. Because no patients were examined at the private retina practice for cataract

surgery, no control patients were derived from that practice. This may have influenced the control patient population demographics.

There is an inherent recall bias associated with a case–control study. In our study, patients with macular holes were probably more likely to recall and correctly identify a family history of macular hole than control patients because they were more familiar with the disorder. Patients were asked to contact their family members if they did not think that they could knowledgeably recall whether the family member had ever been diagnosed with a macular hole. The authors attempted to contact all family members, of both macular hole and control patients, for confirmation of status of macular hole diagnosis; however, many case and control patients were not willing to release relative's contact information, some family members were not willing to participate, and some were deceased. At least one family member was contacted and interviewed in 22% of macular hole patients, and 26% of control patients and no variations from the original findings were uncovered. The incomplete surveillance of family members, lack of direct examination of subjects, and the limited access to medical charts of family members are weaknesses of the study. Regarding the family members with reported macular holes, it was possible to confirm the diagnosis of idiopathic macular hole by chart review in five of these six patients. One patient was not willing to release medical records for review, and the diagnosis was ascertained by phone interview and description of macular hole diagnosis and surgery.

Another inherent limitation in this study is lack of longitudinal follow-up, which may limit the accuracy of uncovering positive family history. We did record ages of family members in both the macular hole and control group, as some individuals may not have reached an at-risk age for disease development. The average age of siblings and children in the macular hole group was 73 and 48, respectively, and 70 and 49 in the control group. As macular hole is a disease typically seen in an elderly population, it is likely that we are missing disease that will develop in family members over time, yet did not exist at the time the data were acquired.

In conclusion, our study found a higher report of macular hole in family members of patients with macular hole; however, regression analysis relates this finding to variables of age and number of family members. Patients with bilateral macular holes had a significantly higher report of family history than those with unilateral macular holes. These findings suggest a possible genetic predisposition to macular hole in some patients. It is likely that nongenetic factors also exist, such as aging and liquefaction of the vitreous. Further studies will need to be done to investigate the attributable portion of any discovered genetic factor in macular hole formation, as the role of environmental factors cannot be discounted. The significantly higher incidence of a family history of macular hole in patients with bilateral (17%) macular hole compared with patients with unilateral (1%) macular hole in our study suggests that this population of patients with bilateral macular holes would be a reasonable target for clinical genetic testing in the future.

Key words: macular hole, genetics, family history, familial, inherited retinal disease, bilateral.

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