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Systemic risk factors for idiopathic macular holes: a case–control study

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Abstract

Purpose/background **The idiopathic full-thickness macular hole (IFTMH) is an important cause of poor vision in the elderly affecting predominantly women over the age of 60 years. While it is accepted that vitreoretinal traction is an important local factor in the development of IFTMH, the underlying cause is not known. The aim of this study was to identify possible systemic risk factors for the development of IFTMH.**

Methods **Two hundred and thirty-seven patients with IFTMH (cases) attending the Macular Hole Clinic at Moorfields Eye Hospital were identified. These were compared with 172 patients without macular holes (controls) attending other clinics in the same hospital. Cases and controls were frequency-matched by sex. The prevalence of the following factors in both groups was ascertained by interview: ethnic origin, place of birth, housing tenure, any systemic diseases, current and lifetime consumption of medication, severe dehydrational episodes, menstrual and obstetric history, onset and severity of menopause and use of exogenous oestrogens (in women only), osteoporosis, vegetarianism, use of vitamin supplementation, and smoking and alcohol consumption. Height and weight were measured for all participants.**

Results **Cases of IFTMH macular holes were predominantly women (67%) and aged 65 years and older (74%). We found very few systemic risk factors that were significantly associated with IFTMH. There was a higher prevalence of diabetes in controls (12% vs 5%). There was no association between the majority of indicators of oestrogen exposure in women and macular holes, but cases had a more difficult menopause as judged by the severity of hot flushes at menopause: odds ratio 2.6 (1.4–4.6).**

Conclusions **In common with other studies, we found only a few systemic factors associated with IFTMH. The study did confirm, however, that IFTMH is a strongly gender-related disease. There is some evidence for the role of sudden changes in hormonal balance, as seen by the increased reporting of severity of symptoms around the menopause along with (statistically non-significant) increased risks associated with hysterectomy and oophorectomy. The particular aetiological factor which puts women at increased risk of macular holes requires further studies.**

Key words Macular holes, Risk factors, Case–control

A full-thickness macular hole is an important cause of poor vision in the elderly. Although in a small number of such patients a specific cause can be identified, such as blunt trauma,[1] cystoid macular oedema[2] or diabetes,[3] the majority of cases appear to be idiopathic in origin. There is increasing evidence that the mechanism responsible for the development and subsequent enlargement of idiopathic full-thickness macular holes (IFTMH) is circumferential vitreoretinal traction.[4] Pars plana vitrectomy, posterior cortical vitreous peeling and intraocular gas tamponade has been shown to be effective in achieving an anatomical closure and visual improvement in eyes with IFTMH.[5–10] In spite of the intense interest in this subject little is known about the systemic risk factors for the development of IFTMH. It is recognised that it affects predominantly women between the ages of 65 and 75 years.[4] There have been conflicting reports on the relationship between the development of IFTMH and previous hysterectomy and/or oophorectomy[11] and the use of exogenous oestrogens such as hormone replacement therapy.[12]

The purpose of this study was to enquire into a number of possible systemic risk factors in a large number of patients with IFTMH (cases) and to compare their responses with those of people without this condition (controls).

Methods

Cases and controls were selected from patients presenting at Moorfields Eye Hospital. Cases were patients with IFTMH presenting at the Macular Hole Clinic in the period from June

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The authors thank all the patients who took part. The study was funded by the Guide Dogs for the Blind Association.

Table 1. *Characteristics of controls*

Clinic attending at hospital	No.	%
Cataract	83	48
Glaucoma	49	28
Retinal	8	5
External diseases	8	5
Other	24	14
Total	172	100

1993 to March 1994. Controls were patients attending other clinics in the hospital in March 1994. All patients underwent a full examination including biomicroscopy. IFTMH was defined as a round or ovoid excavated lesion at the centre of the fovea with an absence of inner retinal tissue in the hole on slit-lamp biomicroscopic examination and confirmed by positive Watzke–Allen test.[13] People with high myopia (>−6 dioptres), age-related macular degeneration, diabetic retinopathy, history of trauma and retinal detachment were excluded from both cases and controls. Controls were frequency-matched for gender and were selected from a similar age-band to cases but were not matched on age. All cases and controls agreed to take part in the study. Data on risk factors were collected over a period of 6 weeks by trained nurses who measured weight and height and administered a questionnaire. As well as standard questions on ethnic group and social class, smoking and alcohol consumption, patients were questioned about their previous medical history and replies coded according to the categories set out in Table 3. Female cases and controls were specifically questioned about their reproductive history, particularly factors associated with endogenous and exogenous oestrogen levels. An attempt at an assessment of the effect of the menopause was made by enquiry into the severity of hot flushes.

In the analysis, the effect of each risk factor was assessed separately using a logistic regression model that included terms for age (<65, 56–74, 75+ years) and sex. Egret statistical software was used for all analyses (version 0.26.6 SERC and CYTEL). Data collected on a continuous scale were also analysed disaggregated (age at menarche, menopause, pregnancies, births, duration of smoking and daily consumption of cigarettes, units of alcohol per week consumed).

Results

A total of 237 cases and 172 controls took part in the study. Controls were mainly identified from cataract and glaucoma clinics (Table 1). The majority of the cases were women (67%) aged 65 years and above (74%) (Table 2). The ratio of men to women was similar at each age group in cases. The control group was similar in respect of gender, as would be expected given that the study was frequency-matched by sex, but patients in this group were slightly older.

Table 3 shows the results of univariate analyses with each risk factor studied. Cases and controls were similar in respect of race and housing tenure. There was no evidence of any association between macular holes and a history of cardiovascular disease, hypertension, asthma and osteoporosis. There was a lower prevalence of diabetes in controls than cases. Cases reported higher levels of atopy and other diseases. There was no association between medication use, dietary factors, smoking and alcohol consumption and macular holes.

There was no association between macular holes and a variety indicators of oestrogen exposure in women: age at menarche and menopause, parity, and use of oestrogen-containing preparations – contraceptive pill and hormone replacement therapy (HRT) (Table 4). More cases than controls reported having had very severe hot flushes at menopause. Hot flushes were associated with use of HRT. Women reporting severe hot flushes around the menopause were nearly 4 times more likely to have taken HRT than women reporting no hot flushes (odds ratio: 3.8, 95% confidence interval: 5–6.4, $p = 0.001$). Adjusting the association between hot flushes and IFTMH by HRT use did not change the observed associations (odds ratio for the association of severe hot flushes with IFTMH adjusted for age and HRT use: 2.3, 95% confidence interval: 1.2–4.1).

Conclusions

Macular holes occur more commonly in women. This finding has been observed in a number of previous studies.[1–4] In our case group 67% were women, which is similar to the proportion observed in the Eye Disease Case Control Study (EDCCS) (72%).[14] In contrast to that study, where a decreasing ratio of women to men was observed with increasing age, we found that the proportion of our case group who were women was

Table 2. *Age and sex of cases and controls*

	Cases			Controls		
	Number	%	% male	Number	%	% male
All ages	237	100	33	172	100	27
<65 years	62	26	31	41	24	41
65–74 years	128	54	33	70	41	24
≥75 years	47	20	35	61	35	21

Cases and controls were frequency-matched on sex.

Table 3. *Association between IFTMH and risk factors studied*

Risk factor		Prevalence in control group (%)	Odds ratio[a]	95% confidence interval
Race	White European	84	1	
	Indian	4	0.9	0.3–2.6
	Other	12	0.8	0.4–1.5
Housing tenure	Owner occupier	61	1	
	Local council tenant	27	0.9	0.6–1.5
	Other	12	0.8	0.4–1.5
Other systemic diseases[b,c]	Diabetes	12	0.3	0.2–0.7
	Cardiovascular disease	18	1.0	0.6–1.7
	Hypertension	34	1.1	0.7–1.7
	Asthma	11	1.1	0.5–2.0
	Atopy	13	1.9	1.1–3.5
	Anaemia	18	1.7	1.0–2.9
	Other	65	2.0	1.2–3.1
Systemic medication[b]	Any	25	0.7	0.5–1.2
	Steroid (ever)	29	0.9	0.5–1.4
	Steroid (currently)	17	1.3	0.7–2.2
Severe dehydrational episodes[b]	Blood transfusion	11	1.8	0.9–3.3
	Severe diarrhoea	20	1.4	0.8–2.2
Osteoporosis[b]	Broken bones	31	1.1	0.7–1.7
	Calcium supplements	7	1.5	0.6–3.3
	Diagnosed osteoporosis	2	2.5	0.7–9.4
Diet[b]	Vegetarian	7	0.9	0.4–2.1
	Eats dairy products	95	2.5	0.8–8.2
	Eats fish	95	0.9	0.3–2.5
	Vitamin supplements	44	1.1	0.7–1.7
Smoking[a]	Current smoker	15	0.9	0.5–1.7
	Ever smoked	58	1.2	0.7–1.9
Alcohol[a]	Current alcohol drinker	62	1.5	0.9–2.5

[a]Derived from a logistic regresion model including terms for age (<65, 65–74, 75+ years) and sex.
[b]Odds ratio reflects comparison with 'null' category.
[c]Reported history: Patients were asked an open-ended question about illness during their lifetime and this was coded appropriately.

similar in all age groups. As our study was hospital-based and moreover was matched for sex we could not directly estimate the association with gender; however, in the general UK population 55% of people of a similar age group to the cases are female.[15] We found a higher prevalence of diabetes in the control group than in the case group. It is not biologically plausible that diabetes may protect against macular holes. This association has probably arisen due to the selection of controls from hospital-based patients.

Such a marked apparent difference in risk of the disease between men and women has not been observed for other age-related eye diseases.[16] One obvious difference between men and women is the dramatic drop

Table 4. *Association between IFTMH and factors pertaining to women*

Risk factor		Prevalence in control group (%)	Odds ratio[a]	95% confidence interval
Menarche	Periods began 13 years or after	73	0.8	0.5–1.5
Parity	One or more pregnancies	78	1.1	0.6–2.0
	One or more births	77	1.0	0.5–1.7
Menopause	Still having periods	5	0.5	0.2–1.6
	Hot flushes			
	None	49	1.0	
	Some	23	1.9	1.0–3.5
	Lots	29	2.6	1.5–4.6
	Hysterectomy	14	1.3	0.7–2.5
	Oophorectomy	9	1.6	0.7–3.4
Use of hormones	Contraceptive pill	8	1.3	0.6–3.2
	Hormone replacement therapy	11	1.5	0.8–3.1
	Tamoxifen	2	2.4	0.5–12.3

[a]Derived from a logistic regression model including terms for age (<65, 65–74, 75+ years).
[b]Odds ratio reflects comparison with 'null' category.

in levels of oestrogen that occur in women at the time of the menopause. Previous studies have suggested an association of macular holes with history of hysterectomy[11] and a protective influence of oestrogen consumption.[12] We examined a variety of factors indicating oestrogen exposure in women. None was statistically significant with the exception of the reported severity of symptoms (hot flushes) around menopause. Subjective perception of the severity of hot flushes may be particularly susceptible to recall bias. It is interesting to note that in contrast to other studies we found use of HRT associated with a non-significant increased risk of macular holes. In the UK, where use of HRT is relatively less common than in other countries such as the USA, this may reflect the fact that women who have more symptoms around the menopause are more likely to be prescribed oestrogen. The overall proportion of patients on HRT in this study is in keeping with the prevalence of this treatment in the general population.[17,18]

Although our study represents the largest group of cases of IFTMH identified at one centre, the study power for some of the factors pertaining to women was low. For factors present in approximately 15% of the female study population (e.g. number of women having had a hysterectomy) the power of the study to detect a twofold increase in risk is 60%; for rarer risk factors occurring in 5% of women (e.g. number still having periods) the power is 25%. This may explain the lack of statistically significant associations. It is interesting to note, however, that women who were still having periods were at less risk of the disease (after controlling for age), and having had a hysterectomy and/or oophorectomy was associated with an increased risk.

It is likely that hormonal influences are important in the aetiology of macular holes. Change in oestrogen levels are known to lead to general vascular and haematological changes[19,20] and may conceivably even influence the composition and/or behaviour of the vitreous or the vitreoretinal interface. It has been observed that higher plasma fibrinogen levels are associated with an increased risk of macular holes, although no obvious explanation for this finding exists.[14]

Given the relatively low prevalence of macular holes in the general population (Blue Mountain Study, Paul Mitchell, personal communication), it is likely that hospital-based case–control studies will continue to be the most feasible way to study the aetiology of this disease, although the interpretation of these studies is not as straightforward as for population-based studies. It is interesting to note that, in common with other case–control studies, relatively few systemic risk factors appeared to be significantly associated with macular holes. Lifestyle factors such as socioeconomic status, smoking, alcohol consumption and dietary factors do not appear to influence the occurrence of this condition. We did not examine any biochemical measures in our sample. In previous studies, however, plasma levels of micronutrients such as antioxidant vitamins have not been associated with IFTMH, in contrast to other age-related eye diseases, such as macular degeneration.[16]

In conclusion, this study provides further evidence that IFTMH is a strongly gender-related disease. Hormones may play an important role, as shown by the increased reporting of severity of symptoms around the menopause along with (statistically non-significant) increased risks associated with hysterectomy and oophorectomy. The specific aetiological factors that put women at increased risk of this disease require further investigation.

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