Prevalence of cystoid macular oedema, epiretinal membrane and cataract in retinitis pigmentosa

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ABSTRACT

Background/Aims To report the prevalence of treatable complications (cystoid macular oedema, CME; epiretinal membrane, ERM and cataract) in patients with retinitis pigmentosa (RP).

Methods Consecutive patients with RP attending a tertiary eye clinic in 2012. Spectral domain-optical coherence tomography was used to determine presence of CME and ERM. Clinic records were reviewed to identify cataract and pseudophakia. Multivariable analyses adjusted for age, gender and other confounders.

Results Data are presented for 338 eyes from 169 patients. CME was present in 58.6% of patients and 50.9% of eyes and was bilateral in 73.7%. ERM, cataract and pseudophakia were present in 22.8%, 23.4% and 11.2% eyes, respectively. In multivariable analyses, CME was associated with younger age (OR 0.81, 95% CI 0.67 to 0.98) but not with gender. Patients with ERM and cataract/pseudophakia were less likely to also have CME (OR 0.19, 95% CI 0.09 to 0.40 and OR 0.37, 95% CI 0.16 to 0.84, respectively). CME was most prevalent in patients with autosomal-dominant inheritance (71.4%), followed by autosomal recessive/sporadic inheritance (58.9%) and least likely in persons with X linked inheritance (12.5%, p<0.001).

Conclusions The prevalence of treatable RP complications is high and suggests it may be clinically beneficial to screen patients with RP to identify those who may benefit from current or future interventions.

INTRODUCTION

Inherited retinal dystrophies are now one of the leading causes of irreversible blindness.[1] Retinitis pigmentosa (RP, OMIM #26800) is the most common group of inherited retinal disorders. Vision loss occurs through progressive loss of photoreceptors and development of complications such as cystoid macular oedema (CME), epiretinal membrane (ERM) and cataract.[2] Treatment of these complications may improve vision[3–5] even if the underlying disorder itself continues to progress. The prevalence of complications is important for planning clinical trials, power calculations and service delivery. The prevalence of CME has been reported from clinic-based surveys to range between 11% and 20% as detected by fluorescein angiography[6 7] and between 5.5% and 49% on optical coherence tomography (OCT).[8–13]

The aim of this study is to report the prevalence of CME, ERM and cataract in a hospital-based sample of patients presenting to a tertiary eye hospital.

METHODS

This is a cross-section prevalence study of patients reviewed in the inherited retinal dystrophy clinics at Moorfields Eye Hospital NHS Foundation Trust, London, UK, from January 2012 to December 2012 inclusive.

Patients were included in the study if they had a consultant (MM, ATM, ARW) confirmed diagnosis of RP or rod cone dystrophy. The diagnosis of RP was based on a history of nyctalopia and evidence of peripheral visual field constriction, characteristic fundus findings on fundus examination, presence of fundus autofluorescence abnormalities such as peripheral hypoautofluorescence and central perimacular hyperautofluorescent rings and full field electroretinogram (ERG) testing in keeping with rod-cone dystrophy. ERG testing was performed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standards.[14] Inheritance pattern was determined from pedigrees and RP was categorised as autosomal dominant (AD) (eg, one affected parent or child, equal gender distribution), autosomal recessive (AR) (eg, no affected parents, consanguinity, simplex cases) and X linked RP (eg, males only, no male-to-male transmission, mothers may have signs). A limited number of patients had a molecular diagnosis. We excluded patients if they had cone rod dystrophy, *ABCA4* retinopathy, X linked retinoschisis, choroideremia, paraneoplastic retinopathy or autoimmune retinopathy. Patients with other causes of CME such as diabetes, retinal vascular occlusion or uveitis were also excluded. Further details are published elsewhere.[15]

The Spectralis HRA +OCT with viewing module V.5.1.2.0 (Heidelberg Engineering, Heidelberg, Germany) was used to acquire autofluorescence and spectral domain-OCT (SD-OCT) images. The SD-OCT protocol used a dense horizontal linear scan centred on the fovea which covered most of the macular region between the vascular arcades. The HEYEX software interface (V.1.6.2.0; Heidelberg Engineering) was used to view and analyse images. OCT images were scrutinised for the presence of CME which was defined as the presence of hyporeflective cystic spaces on two or more consecutive macular raster scans. Presence of ERM was defined from OCT images as hyper-reflectivity of

Table 1 Baseline characteristics of cohort

Characteristics	Number or %
Age, years (SD)	47.1 (±18.4)
Male (%)	46.8%
Autosomal dominant (%)	42 (24.9%)
RP1	11
RHO	6
PRPF31	3
RP11	3
PRPF8	2
RDS	2
RP9	1
Unknown/not tested	14
Autosomal recessive/sporadic (%)	112 (66.3%)
USH2A	10
MYO7A	3
USH1C	2
CRB1	2
Unknown/not tested	95
X linked (%)	8 (4.7%)
RPGR	6
Unknown/not tested	2
Unclear inheritance	7 (4.1%)

Autosomal dominant, autosomal recessive and X linked were determined clinically, with molecular confirmation in some patients.

the innermost retinal layer with or without foveal anatomical distortion. Lens status was assessed from clinical notes and pseudophakia was confirmed from clinical or surgical records.

Statistical analyses

SAS V.9.2 (SAS, Cary, North Carolina) was used for analyses. Fisher's exact test was used for comparing categorical variables, while the Student's t-test and ANOVA were used for comparing continuous variables. Logistic regression models by subject were used to perform multivariable analyses adjusting for age, gender and other factors at the patient level. Results were considered significant at $p<0.05$. OR and 95% CI are provided.

RESULTS

There were 169 patients and 338 eyes included in this study. The mean age of patients was 47.1 years (±18.4) (table 1). Males comprised 46.8% of patients. The majority of patients had autosomal recessive/sporadic inheritance and mutations in *RP1* and *USH2A* were the most common cause identified among those patients who underwent genetic testing.

CME was present in 58.6% of patients and 50.9% of eyes. Of these patients, 73.7% had bilateral CME (table 2). ERM was present in 25.4% of patients and 22.8% of eyes and was bilateral in 79.1% patients. Cataract was present in 27.2% of patients, 23.4% of eyes and bilateral in 71.7% patients. Pseudophakia was present in 11.8% of patients, 11.2% of eyes and was bilateral in 95% of patients. Among patients with CME, 31.3% were mild enough that they were not treated, 37.4% were currently being treated with oral acetazolamide, 29.3% with topical dorzolamide and 2% had been previously treated. The inverse association with CME prevalence and age persists after controlling for inheritance pattern.

In table 3, multivariable age-gender adjusted associations are reported. CME was associated with younger age (OR 0.81, 95% CI 0.67 to 0.98) but not with gender. CME was most prevalent

Table 2 Prevalence of cystoid macular oedema, epiretinal membrane and cataract

	By patient, N (%)	By eye, N (%)
All patients	169	338
Cystoid macular oedema	99 (58.6)	172 (50.9)
Bilateral	73 (73.7)	–
Untreated	31 (31.3)	53 (30.8)
Oral acetazolamide	37 (37.4)	68 (39.5)
Topical dorzolamide	29 (29.3)	49 (28.5)
Past treatment	2 (2.0)	2 (1.2)
Epiretinal membrane	43 (25.4)	77 (22.8)
Bilateral	34 (79.1)	–
Cataract	46 (27.2)	79 (23.4)
Bilateral	33 (71.7)	–
Pseudophakia	20 (11.8)	38 (11.2)
Bilateral	19 (95.0)	–

in patients with AD inheritance (71.4% with CME in at least one eye), followed by AR/sporadic inheritance (58.9%) and was least likely in those with X linked inheritance (12.5%, $p<0.001$). The OR for having CME in X linked inheritance was 0.05 95% CI 0.006 to 0.48). Patients with ERM and cataract/pseudophakia were less likely to also have CME (OR 0.19 95% CI 0.09 to 0.40 and OR 0.37, 95% CI 0.16 to 0.84, respectively).

DISCUSSION

The burden of blindness from inherited retinal dystrophies such as RP is increasing,[1] due partly to the lack of effective treatments for this group of disorders. A number of sight impairing complications are associated with RP, and vision outcome may be improved when these complications are identified and treated. We report that in a hospital-based sample of 169 patients with RP (338 eyes), the prevalence of CME, ERM, cataract and pseudophakia in eyes was 50.9%, 22.8%, 23.4% and 13.6%, respectively. If one eye had an RP complication, the other eye was also highly likely to be involved (>70%). These data suggest a relatively high prevalence of potentially treatable complications and suggests it is worthwhile screening patients with RP, including with OCT, regularly to detect these conditions.

Our prevalence findings for CME are similar to the higher estimates reported by other investigators. A trial of 39 patients by Adackapara *et al*[8] recruited to test the efficacy of lutein supplements in RP reported a CME prevalence of 49% in patients (and 47% in eyes) at baseline. Another clinic-based study by Hajali *et al*[10] of consecutive patients with RP reported a lower CME prevalence of 38% in 124 patients, of whom 27% had bilateral CME. One reason for the lower prevalence reported in the study by Hajali *et al*[10] may be the stricter definition of CME used, where more than one cystoid space was required to define CME. Similar studies using this definition have also reported lower prevalence of CME in patients, for example, that by Testa *et al*[16] which reported CME prevalence of 22.9%. The study by Testa *et al*[16] excluded patients with Usher syndrome, which comprised a large proportion of our patients with RP and may partly contribute to the lower estimate. Other studies reporting lower estimates used time-domain OCT which may have missed small cystoid spaces due to the resolution on time domain. For example, Hagiwara *et al*[9] using time domain OCT reported a prevalence of macular cysts as low as 5.5%. Studies using a similar definition to that used in our study have reported CME prevalence of 26.9% to 49%.[8 11]

Table 3 Associations with cystoid macular oedema, epiretinal membrane and cataract

	Cystoid macular oedema	Epiretinal membrane	Cataract/pseudophakia
	OR (95% CI)*		
Age, per 10 years increase	**0.81 (0.67 to 0.98)**	1.13 (0.91 to 1.39)	**2.30 (1.68 to 3.14)**
Male vs female	1.12 (0.60 to 2.09)	0.99 (0.48 to 2.05)	0.71 (0.32 to 1.59)
Inheritance pattern			
AR/sporadic	1.0 (reference)	1.0	1.0
AD	2.00 (0.90 to 4.43)	0.93 (0.40 to 2.13)	0.41 (0.16 to 1.10)
XL	**0.05 (0.006 to 0.48)†**	4.73 (0.93 to 24.01)	0.38 (0.04 to 3.90)
Cystoid macular oedema	–	–	–
Epiretinal membrane	**0.19 (0.09 to 0.40)†**	–	–
Cataract/pseudophakia	**0.37 (0.16 to 0.84)†**	–	–

Bolded values are significant at p<0.05
*Adjusted for age. Gender was not significantly associated in any analyses.
†Additionally adjusted for other variables significant in univariable analyses that is, age, inheritance pattern, epiretinal membrane and cataract/pseudophakia.
AD, autosomal dominant; AR, autosomal recessive; XL, X linked.

We report ERM prevalence of 22.8% among eyes in our study. A wide range of ERM prevalence in eyes with RP and detected using OCT has been reported, ranging from 0.6%, 15.6%, 27.3% to 64.3%.[9 13 16 17] The highest prevalence was reported by Grigoropoulos *et al*[17] who studied patients with advanced RP and used time domain OCT, which may account for the different estimates. Hagiwara *et al*[9] reported the lowest ERM prevalence of 0.6% using time domain OCT which is less sensitive than the SD-OCT used in our study.

There are limited data on the prevalence of cataract in eyes with RP. We found 23.4% of eyes had cataract, while 13.6% were pseudophakic. This compares with a reported cataract and pseudophakia/aphakia prevalence of 36.8% and 15.4% in eyes with RP by Testa *et al*[16] from an Italian population and 44.4% with posterior subcapsular cataract in a Japanese population.[18] Rates of pseudophakia may not be directly comparable across different countries due to different health systems and thresholds for cataract surgery.

Few studies have reported on the associations of CME. Knowledge of associations is useful in providing insights into the underlying pathophysiology, which remains an area of active research.[19] We found CME was associated with younger age, more likely in AD inheritance and least in X linked inheritance and less likely in the presence of ERM or cataract. That CME is less likely in older patients has been suggested,[20 21] but not previously demonstrated in clinical studies. A positive association with AD inheritance but negative with X linked inheritance has also been reported by Sandberg *et al* and Testa *et al*,[16 22] which Hajali *et al*[10] found as well, although the result was not statistically significant in the study of Hajali *et al*.[10] Finally, Testa *et al*[16] have also reported that CME is less likely in patients who are pseudophakic, as in our study. These results suggest that the pathophysiological process leading to CME in RP may differ from that leading to cataract and ERM, as the conditions do not appear to frequently coexist, unlike in other retinal disorders such as diabetic retinopathy.[23] Our results support the hypothesis that relatively healthy retinal tissue is required to cause CME, for example, through dysfunction of Muller cell osmoregulation,[19] which would explain why younger patients and milder forms of RP (such as AD forms) are more likely to have CME than more severe forms (X linked RP). This would also explain the inverse association between CME and ERM as well as cataract, as the latter two conditions occur in later life, when there is less healthy retinal tissue remaining.

Strengths of this study include its moderately large sample size, systematic evaluation of CME and ERM according to a prespecified protocol and multivariable adjustment for age and other confounders. Limitations include that lens status was determined from clinical records, with variability in documentation of cataract status. Severity and type of cataract were not documented. The status of pseudophakia, however, is robust as this was checked from surgical records. We combined simplex inheritance cases with AR in our analyses, which may have included de novo mutations and introduced some misclassification into this category. This misclassification is likely to be small as the majority of simplex cases are later found to have AR inheritance.[2] The prevalence estimates from this study do not apply to all patients with RP and are likely higher than the true population prevalence of RP complications. However, these estimates are clinically relevant as they derive from a sample of patients presenting to tertiary eye clinics, which is how most patients with RP are managed and where recruitment would occur for clinical trials of new therapies. The prevalence estimates reported here will be of value in power calculations and trial design.

In conclusion, we report that the prevalence of RP complications in a tertiary eye hospital setting is high, with many cases showing bilateral involvement. Younger age, AD inheritance and the absence of ERM and cataract/pseudophakia were associated with increased risk of CME. The high prevalence of treatable RP complications suggests it may be clinically beneficial for eye care professionals to screen patients with RP with SD-OCT on a regular basis to identify those who may benefit from current or future interventions.

Contributors GL, ATM, ARW and MM conceived the study idea. GL, MM, SS, PB and PS designed the study and collected data. AK and GL performed statistical analyses. GL drafted the initial manuscript. GL, SS, PB, PS, ATM, ARW, PM, AK and MM all reviewed the draft and provided critical evaluations and improvements.

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