Prevalence of Cystoid Macular Edema, Epiretinal Membrane and Cataract in Retinitis Pigmentosa

Short title: CME, ERM and cataract in retinitis pigmentosa

Gerald Liew, PhD,[1,2] Stacey Strong MD,[2,3] Patrick Bradley MD,[2] Philip Severn MD, [2,4] Anthony T. Moore, PhD,[2,3,5] Andrew R. Webster, PhD,[2,3] Paul Mitchell PhD,[1] Annette Kifley MStat,[1] Michel Michaelides, PhD.[2,3]

[1] Centre for Vision Research, Westmead Institute for Medical Research, University of Sydney, Sydney, Australia

[2] Moorfields Eye Hospital, London, EC1V 2PD, UK

[3] University College London, Institute of Ophthalmology, Bath Street, London, EC1V 9EL, UK

[4] South Tees Hospital NHS Foundation Trust, Middlesbrough, TS4 3BW, UK

5. Ophthalmology Department UCSF School of Medicine San Francisco USA

Financial Disclosure(s):

The authors have no proprietary or commercial interest in any materials discussed in this article.

Corresponding author

Michel Michaelides, University College London, Institute of Ophthalmology, Bath Street, London EC1V 9EL, UK. Tel: +44 20 76086864, E-mail: michel.michaelides@ucl.ac.uk

Word count Text: 1831

Word count Abstract: 224

ABSTRACT

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

Methods: Consecutive RP patients attending a tertiary eye clinic in 2012. Spectral domain-optical coherence tomography (SD-OCT) 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 (Odds Ratio, OR 0.81, 95% Confidence Interval, CI 0.67, 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, 0.40 and OR 0.37, 95% CI 0.16, 0.84, respectively). CME was most prevalent in patients with autosomal dominant inheritance (71.4%), followed by AR/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 RP patients 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 edema (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. The study was approved by the Human Research Ethics Committee of Moorfields Eye Hospital NHS Foundation Trust.

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

hypoautofluoresence and central peri-macular 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 (e.g. one affected parent or child, equal gender distribution), autosomal recessive (e.g. no affected parents, consanguinity, simplex cases) and X-linked RP (e.g. 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 version 5.1.2.0 (Heidelberg Engineering, Heidelberg, Germany) was used to acquire autofluorescence and SD-OCT images. The SD-OCT protocol utilized a dense horizontal linear scan centered on the fovea which covered most of the macular region between the vascular arcades. The HEYEX software interface (version 1.6.2.0; Heidelberg Engineering) was used to view and analyzee images. OCT images were scrutinized 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 hyperreflectivity of 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 version 9.2 (SAS Institute, Cary NC) was used for analyses. Fishers' 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. Odds ratios (OR) and 95% confidence intervals (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.

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.

SD refers to standard deviation.

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.

Table 2. Prevalence of cystoid macular edema, epiretinal membrane and cataract

	By patient, N (%)	**By Eye, N (%)**
All patients	169	338
Cystoid macular edema	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 **Table 3**, multivariable age-gender adjusted associations are reported. CME was associated

with younger age (OR 0.81, 95% CI 0.67, 0.98) but not with gender. CME was most

prevalent 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, 0.48). Patients with ERM and cataract/pseudophakia were less likely to also have CME (OR 0.19 95% CI 0.09, 0.40 and OR 0.37, 95% CI 0.16, 0.84 respectively).

Table 3. Associations with cystoid macular edema, epiretinal membrane and cataract

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

AD refers to autosomal dominant; AR to autosomal recessive; XL to X–linked; CI to confidence intervals;

* Adjusted for age. Gender was not significantly associated in any analyses.
** Additionally adjusted for other variables significant in univariable analyses i.e.age, inheritance pattern, epiretinal membrane and cataract/pseudophakia.

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 RP patients (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 RP patients, 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]

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%.[9,16,13,17] The highest prevalence was reported by Grigoropoulos et.al [17] who studied patients with advanced RP and utilized 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,[22,16] 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 co-exist, 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 2 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 pre-specified 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 was 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 RP patients 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 RP patients 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 RP patients with SD-OCT on a

regular basis to identify those who may benefit from current or future interventions.

Author contributions

GL, ATM, ARW, MM conceived the study idea; GL, MM, SS, PB, PS designed the study

and collected data; AK, GL performed statistical analyses; GL drafted the initial manuscript;

GL, SS, PB, PS, ATM, ARW, PM, AK, MM all reviewed the draft and provided critical

evaluations and improvements.

REFERENCES

1. Liew G, Michaelides M, Bunce C. A comparison of the causes of blindness certifications in England and Wales in working age adults (16-64 years), 1999-2000 with 2009-2010. *BMJ Open.* 2014;4:e004015.

2. Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. *Lancet* 2006;368:1795-809.

3. Dikopf MS, Chow CC, Mieler WF, et al. Cataract extraction outcomes and the prevalence of zonular insufficiency in retinitis pigmentosa. *Am.J.Ophthalmol.* 2013;156:82-8.

4. Ikeda Y, Yoshida N, Murakami Y, Nakatake S, Notomi S, Hisatomi T et al. Long-term Surgical Outcomes of Epiretinal Membrane in Patients with Retinitis Pigmentosa. *Sci.Rep.* 2015;5:13078.

5. Strong SA, Gurbaxani A, Michaelides M. Treatment of Retinitis Pigmentosa-Associated Cystoid Macular Oedema Using Intravitreal Aflibercept (Eylea) despite Minimal Response to Ranibizumab (Lucentis): A Case Report. *Case.Rep.Ophthalmol.* 2016;7:389-97.

6. Newsome DA. Retinal fluorescein leakage in retinitis pigmentosa. *Am.J.Ophthalmol.* 1986;101:354-60.

7. Pruett RC. Retinitis pigmentosa: clinical observations and correlations. *Trans.Am.Ophthalmol.Soc.* 1983;81:693-735.

8. Adackapara CA, Sunness JS, Dibernardo CW, et al. Prevalence of cystoid macular edema and stability in oct retinal thickness in eyes with retinitis pigmentosa during a 48-week lutein trial. *Retina* 2008;28:103-10.

9. Hagiwara A, Yamamoto S, Ogata K, et al. Macular abnormalities in patients with retinitis pigmentosa: prevalence on OCT examination and outcomes of vitreoretinal surgery. *Acta Ophthalmol.* 2011;89:e122-e125.

10. Hajali M, Fishman GA, Anderson RJ. The prevalence of cystoid macular oedema in retinitis pigmentosa patients determined by optical coherence tomography. *Br.J.Ophthalmol.* 2008;92:1065-8.

11. Makiyama Y, Oishi A, Otani A, et al. Prevalence and spatial distribution of cystoid spaces in retinitis pigmentosa: investigation with spectral domain optical coherence tomography. *Retina* 2014;34:981-8.

12. Testa F, Melillo P, Rossi S, et al. Prevalence of macular abnormalities assessed by optical coherence tomography in patients with Usher syndrome. *Ophthalmic Genet.* 2018;39:17-21.

13. Triolo G, Pierro L, Parodi MB, et al. Spectral domain optical coherence tomography findings in patients with retinitis pigmentosa. *Ophthalmic Res.* 2013;50:160-4.

14. McCulloch DL, Marmor MF, Brigell MG, et al. ISCEV Standard for full-field clinical electroretinography (2015 update). *Doc.Ophthalmol.* 2015;130:1-12.

15. Liew G, Moore AT, Webster AR, et al. Efficacy and prognostic factors of response to carbonic anhydrase inhibitors in management of cystoid macular edema in retinitis pigmentosa. *Invest Ophthalmol.Vis.Sci.* 2015;56:1531-6.

16. Testa F, Rossi S, Colucci R, et al. Macular abnormalities in Italian patients with retinitis pigmentosa. *Br.J.Ophthalmol.* 2014;98:946-50.

17. Grigoropoulos VG, Emfietzoglou J, Nikolaidis P, et al. Optical coherence tomography findings in patients with retinitis pigmentosa and low visual acuity. *Ophthalmic Surg.Lasers Imaging* 2010;41:35-9.

18. Fujiwara K, Ikeda Y, Murukami Y, et al. Risk factors for posterior subcapsular cataract in retinitis pigmentosa. *Invest Ophthalmol Vis Sci* 2017;58:2534-37

19. Strong S, Liew G, Michaelides M. Retinitis pigmentosa-associated cystoid macular oedema: pathogenesis and avenues of intervention. *Br.J.Ophthalmol.* 2017;101:31-7.

20. Lupo S, Grenga PL, Vingolo EM. Fourier-domain optical coherence tomography and microperimetry findings in retinitis pigmentosa. *Am.J.Ophthalmol.* 2011;151:106-11.

21. Mrejen S, Audo I, Bonnel S, et al. Retinitis Pigmentosa and Other Dystrophies. *Dev.Ophthalmol.* 2017;58:191-201.

22. Sandberg MA, Brockhurst RJ, Gaudio AR, et al. Visual acuity is related to parafoveal retinal thickness in patients with retinitis pigmentosa and macular cysts. *Invest Ophthalmol Vis Sci* 2008;49:4568-72

23. Akbar KI, Mohamed MD, Mann SS, et al. Prevalence of vitreomacular interface abnormalities on spectral domain optical coherence tomography of patients undergoing macular photocoagulation for centre involving diabetic macular oedema. *Br.J.Ophthalmol.* 2015;99:1078-81.