

Bullous X-Linked Retinoschisis: Clinical Features and Prognosis

Anne-Marie Hinds FRCOphth^{*1,2}, Abigail Fahim MD, PhD^{*3}, Anthony T. Moore FRCOphth^{1,2}, Sui Chien Wong FRCOphth¹, Michel Michaelides FRCOphth^{1,2}

1. Moorfields Eye Hospital, 162 City Road, London, EC1V 2PD, UK

2. UCL Institute of Ophthalmology, 11-43 Bath Street, London, EC1V 9EL, UK

3. Kellogg Eye Center, University of Michigan, Ann Arbor, MI, USA

*These authors contributed to this work equally.

Corresponding Author:

Michel Michaelides
Moorfields Eye Hospital,
162 City Road,
London,
EC1V 2PD. UK
Telephone: +44 20 7608 6864
Email: michel.michaelides@ucl.ac.uk

Word Count: 1,375

SYNOPSIS:

In a series of 9 patients with X-linked retinoschisis and bullous schisis cavities, associated ocular features included strabismus, vitreous haemorrhage, nystagmus, and persistent foetal vasculature. Retinal detachment was seen in 4 out of 18 eyes.

ABSTRACT

Background/Aims: A subset of patients with X-linked retinoschisis (XLRS) have bullous schisis cavities in the peripheral retina. This study describes the characteristics and prognosis of the bullous form of XLRS.

Methods: A retrospective case series was performed of 9 patients with molecularly proven bullous XLRS seen at a single tertiary centre.

Results: All cases of bullous peripheral schisis were bilateral; with 1 unilateral case at presentation which developed into bilateral bullous schisis over time. The mean age of onset was 1.9 years (range: 1 month – 7 years, SD: 2.1 years) and at clinical diagnosis was 5.9 years (range: 1 month – 27 years, SD: 9.0 years). Mean follow-up was 11 years (range: 6 months – 36 years, SD: 10.8 years). Strabismus was the most common presentation (n=7). Other presenting complaints included decreased vision, floaters and an irregularly shaped pupil. The most frequently associated ocular features were strabismus (100%), vitreous haemorrhage (4/18 eyes, 22%), nystagmus (2/9, 22%) and persistent foetal vasculature (1/18, 6%). Localised tractional detachment was seen in 2/18 (11%) eyes, total detachment that underwent surgical repair in 1/18 (6%) and pigmented demarcation lines in a further 22% of eyes. There was 1 eye with exudative retinal detachment.

Conclusion: In XLRS, bullous schisis may be congenital or develop soon after birth and most commonly presents with strabismus. Cases may be complicated by some form of retinal detachment, which may be tractional or a Coats-like exudative detachment.

INTRODUCTION

X-linked Retinoschisis (XLRs) is a congenital, hereditary disease characterised by foveal schisis in the majority of affected males¹. XLRs is caused by pathological variants in the *RS1* gene on Xp22.2, which encodes the secreted protein retinoschisin (RS), involved in cellular adhesion and cell-cell interactions within the inner nuclear layer as well as synaptic connections between photoreceptors and bipolar cells.

Peripheral schisis is seen in 33-60% of affected individuals¹⁻⁶. Some authors believe that bullous retinoschisis represents the early stage of the disease followed by spontaneous resolution within the first several years of life^{7 8}. Supporting this is the fact that bullous peripheral schisis is rarely seen in adults with XLRs¹.

Bullous schisis tends to resolve, often leaving a pigmented demarcation line in the majority of eyes^{9 10}. Such pigmented demarcation lines are thought to represent a significant period of stasis at the edge of chronic retinal detachment when seen in older individuals, but this is unlikely to be the case in bullous schisis. Retinal detachment is reported to complicate 5-22% of XLRs cases though it is not clear from the literature if this is more common in eyes with bullous schisis^{1-3 5 6 11}.

We present the largest series to date describing the clinical characteristics and outcome in a series of patients with XLRs who presented with large bullous schisis.

METHODS

Patient databases of paediatric genetic clinics at Moorfields Eye Hospital were searched for all patients whose correspondence contained the terms bullous, congenital, hereditary, X-linked, sex linked, genetic, retinoschisis. The genetics database was searched for all patients with confirmed *RS1* mutation and documented peripheral schisis. The following data were extracted from the case notes: demographics, visual acuity, date at last follow-up, refraction, retinal examination findings, other ocular and systemic findings, results of any ocular investigations and ophthalmic treatment. For analysis, Snellen acuity was converted to logMAR using standard conversion tables. Counting fingers (CF) and Hand Motions (HM) at 1/3m were taken as 2.0 and 3.0 logMAR respectively. Acuities of Perception of Light (PL) or worse were excluded from analysis.

Microsoft Excel®, Microsoft Office Professional Plus 2013, Microsoft Corporation, Washington and IBM® SPSS® statistics version 21, IBM Corp, New York were used for statistical analysis.

RESULTS

Nine patients were identified with bullous schisis. The average age of onset was 1.9 years (range: 1 month – 7 years, SD: 2.1 years) and at clinical diagnosis was 5.9 years (range: 1 month – 27 years, SD: 9.0 years). Mean visual acuity at final follow-up was 1.1 logMAR (range: 0.0 to 3.0, SD: 0.9), with 5 patients registered as sight impaired or severely sight impaired. One patient had PL vision, and that eye was excluded from analysis. The mean refractive error was +5.50 DS (n=7, range: +0.26

DS to +10.25 DS, SD: 4.0 DS). Patients were followed for an average of 10 years (range: 6 months – 36 years, SD: 10.8 years). A family history of XLRS was present in 4 cases. All cases had a hemizygous mutation in the *RS1* gene. No two cases had the same genetic mutation (Table 1).

In all cases the bullous schisis cavities were bilateral and located inferiorly. One patient initially presented at 7 weeks of age with unilateral inferior bullous retinoschisis, and the unilateral nature presented a diagnostic challenge. Inferior bullous schisis subsequently developed in the contralateral eye at age 4 months. The most common associated ocular features were strabismus (100% of patients), vitreous haemorrhage (4/18 eyes, 22%), nystagmus (2/9 patients, 22%) and persistent foetal vasculature (1/18 eyes, 6%). Strabismus was also the most common presenting sign: 7/9 cases. Other presenting complaints were decreased vision, floaters and an irregularly shaped pupil.

All eyes had macular pathology in the form of schisis (10/18, 56%), bullous schisis or detachment involving the macula (6/18, 33%), and late scarring or atrophic changes in older patients (2/18, 11%).

Two (11%) eyes in 2 different patients developed tractional retinal detachment and visual acuities were poor in these eyes (range: 1.6 to CF)(Figure 1A). One of these patients had tractional detachment in the right eye with CF vision and exudative detachment in the left eye with final vision of 1.0 (Figure 1C). Surgical repair was carried out in a 3rd patient with total retinal detachment in 1 eye and the final vision was PL. The visual acuity was similar in eyes with retinal detachment (mean 1.8, SD 0.28) and without (mean 1.1, SD 0.88), $p=0.26$. In 4 eyes, while no retinal detachment was seen, there was a pigmented demarcation line (Figure 1B). Vitreous haemorrhage was seen in 4/18 (22%) eyes.

DISCUSSION

Bullous schisis cavities may spontaneously resolve in early childhood, leaving a pigmented demarcation line in 85 – 100% of cases^{9 10}. Demarcation lines are traditionally thought to be caused by proliferation of retinal pigment epithelium at the junction of flat and detached retina¹². Such demarcation lines were seen in only 4 of 18 eyes in this study. At the time of last follow up bullous schisis had still not resolved in 10/12 eyes of 6 boys ranging in age from 11 months to 14 years.

Previous papers reported the rate of retinal detachment in any form of XLRS as between 5 and 22%^{1-3 5 6 11}. One series of 5 cases looking specifically at the bullous form reported no cases of retinal detachment and no studies to date have looked specifically at retinal detachment rates in bullous XLRS⁹. Two eyes in the current study developed localised tractional detachment and a 3rd had surgical repair for total retinal detachment.

The role of retinal detachment surgery in bullous XLRS is uncertain, considering 1 operated patient ended with PL vision, and the 2 unoperated eyes had 1.6 and CF vision. Also, eyes with and without detachment had similar acuities. Retinal detachment repair in XLRS patients presents technical challenges due to the relative fragility of the retina, which may affect surgical outcomes. The chronicity of a detachment and the presence of proliferative vitreoretinopathy (PVR) are additional

Table 1. Demographic and clinical characteristics of patients with bullous peripheral schisis

Patient #	Age at clinical Diagnosis (years)	Length of follow-up (years)	Mutation	Average spherical equivalent	LogMAR visual acuity Right Eye	LogMAR visual acuity Left Eye	Presentation	Peripheral Retinal Findings (Right)	Peripheral Retinal Findings (Left)
1	0.1	0.6	c.589C>T (p.Arg197Cys)	9.8	3.0	3.0	Irregularly shaped pupil, esotropia	Inferior bullous schisis obscuring macula at presentation	Inferior bullous schisis obscuring macula which developed 2 months after initial presentation
2	1.25	9.2	c.35T>A (p.Leu12His)	2.6	1.1	0.6	Esotropia	Inferior bullous schisis with demarcation line + PFV ^a	Previous bullous schisis flattened to shallow schisis
3	1.5	8.6	c.598C>T	7.5	0.8	1.3	Esotropia	Infero-temporal bullous schisis	Infero-temporal bullous schisis
4	0.92	13.4	c.620A>C	1.5	0.7	PL	Exotropia	Inferior bullous schisis	Total retinal detachment (tractional)
5	14	36.0	c.305G>A (p.Arg102Gln)	Not available	0.3	0.0	Floater	Previous inferior bullous schisis (now resolved)	Previous bullous inferior schisis through macula (now resolved)
6	3	2.5	c.236G>C (p.Gly109Ala)	10.3	1.0	1.0	Esotropia	Previous inferior bullous schisis through macula	Previous inferior bullous schisis through macula
7	3	0.5	Deletion of exons 4-5	Not available	1.1	0.9	Reduced vision, esotropia	Bullous inferior schisis with a demarcation line	Bullous inferior schisis through macula
8		7.5	c.496T>C (p.Tyr166His)	0.56	0.0	1.6	Esotropia	Infero-temporal bullous schisis	Localised posterior pole and peri-papillary tractional detachment as well as schisis
9	27	9.6	c.574C>T (p.Pro192Ser)	6.25	2.0	1.0	Strabismus	Tractional detachment nasal to disc and 360° ridge retinal detachment at equator as well as schisis	Peripheral exudative detachment

^a PFV = Persistent Foetal Vasculature. Nucleotide and amino acid positions refer to ensembl transcript ENST00000379984.

factors to consider when deciding whether to operate, as with all retinal detachments, but particularly in XLRS patients given the poor functional outcomes with retinal detachment repair overall. In the future if a gene therapy is approved for use in XLRS patients, the combination of detachment repair and gene therapy could possibly provide better outcomes for these patients.

Other characteristics were similar to those found in the series by George et al⁹. Average visual acuity was LogMAR 1.4 (Snellen 20/500) compared to LogMAR 1.1 (Snellen 20/250) in our study. Based on the fact that nystagmus developed 2 – 15 months after birth in their series, George et al suggested that the bullous schisis may not have been present at birth. This phenomenon is confirmed by 1 patient in our series, who presented with unilateral bullous schisis and later developed bilateral schisis at age 4 months. Despite bullous schisis overriding the macula bilaterally this child did not have nystagmus.

The dark-adapted bright flash electroretinogram (ERG) has been well established as a diagnostic tool in XLRS¹³. An electronegative waveform is classic, although not universal, and the b to a wave ratio varies¹³. However, ERG has limitations in children due to reliability and large test-retest variability, made worse in cases of strabismus and nystagmus, and we do not present ERG data here. However, future investigations of the dark-adapted bright flash ERG in patients with peripheral schisis may reveal important associations.

It was unsurprising that no specific genetic mutation was more common in patients with bullous XLRS. There are more than 80 different known disease-causing sequence variants in *RS1* and the retinoschisis consortium noted that, “Despite the enormous mutation heterogeneity, patients have relatively uniform clinical manifestations, although with great intra-familial variation in age at onset and progression.”¹⁴

This study shows that bullous peripheral schisis in XLRS may be congenital or develop soon after birth and most commonly presents with strabismus. Patients may develop some form of retinal detachment whether tractional detachment or a Coats-like exudative detachment. To our knowledge, only case reports and one previous series in the English Language literature looked specifically at the characteristics of bullous XLRS⁹. This current study investigated more patients with longer follow-up and only included molecularly proven cases. It, therefore, further contributes to the body of knowledge on this rare presentation as well as highlights questions for further study.

ACKNOWLEDGMENTS

This work was supported by the National Institute for Health Research Biomedical Research Centre, grant number BRC2_001, Moorfields Eye Hospital Special Trustees, grant number ST 13 10 F, Moorfields Eye Charity, grant number MEC 13 10 A, and the Foundation Fighting Blindness, grant number CD-CL-0711-0518-UCL. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. The authors acknowledge Melissa Kasilian for assistance in figure preparation.

COMPETING INTERESTS

Abigail Fahim owns stock in Ionis Pharmaceuticals (Carlsbad, CA). Michel Michaelides consults for Meira GTx (London, UK), Ora Inc (Andover, MA), and Shire (Hampshire, UK). Anne-Marie Hinds and Anthony Moore have no financial disclosures.

CONTRIBUTORSHIP

The authors contributed in the following ways to this manuscript:

Anne-Marie Hinds participated in study design, data collection, and manuscript preparation. Abigail Fahim participated in data collection and manuscript preparation. Anthony Moore participated in data collection. Michel Michaelides participated in study design, data collection, and manuscript editing.

REFERENCES

1. Tantri A, Vrabec TR, Cu-Unjieng A, et al. X-linked retinoschisis: a clinical and molecular genetic review. *Surv Ophthalmol* 2004;49(2):214-30. doi: 10.1016/j.survophthal.2003.12.007
2. George ND, Yates JR, Moore AT. Clinical features in affected males with X-linked retinoschisis. *Arch Ophthalmol* 1996;114(3):274-80.
3. Wang NK, Liu L, Chen HM, et al. Clinical presentations of X-linked retinoschisis in Taiwanese patients confirmed with genetic sequencing. *Mol Vis* 2015;21:487-501.
4. Deutman A. Sex-linked juvenile retinoschisis. In: Deutman AF, ed. *The Hereditary Dystrophies of the Posterior Pole of the Eye*. Assen, The Netherlands: Van Gorcum 1971:48-98.
5. Roesch MT, Ewing CC, Gibson AE, et al. The natural history of X-linked retinoschisis. *Can J Ophthalmol* 1998;33(3):149-58.
6. Fahim AT, Ali N, Blachley T, et al. Peripheral fundus findings in X-linked retinoschisis. *Br J Ophthalmol* 2017 doi: 10.1136/bjophthalmol-2016-310110 [published Online First: 2017/03/27]
7. Kawano K, Tanaka K, Murakami F, et al. Congenital hereditary retinoschisis: evolution at the initial stage. *Albrecht Von Graefes Arch Klin Exp Ophthalmol* 1981;217(4):315-23.
8. Turut P, François P, Castier P, et al. Analysis of results in the treatment of peripheral retinoschisis in sex-linked congenital retinoschisis. *Graefes Arch Clin Exp Ophthalmol* 1989;227(4):328-31.
9. George ND, Yates JR, Bradshaw K, et al. Infantile presentation of X linked retinoschisis. *Br J Ophthalmol* 1995;79(7):653-7.
10. Mosin IM, Moshetova LK, Mishustin VV, et al. [Bullous form of X-linked congenital retinoschisis in infants]. *Vestn Oftalmol* 2001;117(1):40-3.
11. Kellner U, Brummer S, Foerster MH, et al. X-linked congenital retinoschisis. *Graefes Arch Clin Exp Ophthalmol* 1990;228(5):432-7.
12. Retinal Detachment. In: Kanski J, ed. *Clinical Ophthalmology*. Philadelphia: Elsevier 2007:698-712.
13. Vincent A, Robson AG, Neveu MM, et al. A phenotype-genotype correlation study of X-linked retinoschisis. *Ophthalmology* 2013;120(7):1454-64. doi: 10.1016/j.ophtha.2012.12.008
14. Functional implications of the spectrum of mutations found in 234 cases with X-linked juvenile retinoschisis. The Retinoschisis Consortium. *Hum Mol Genet* 1998;7(7):1185-92.