

Surgical management of non-syndromic ectopia lentis

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Abstract

• **AIM:** To compare whether aphakic contact lenses or secondary iris-claw intraocular lenses are superior in the refractive management post-pars plana vitreolensectomy in a pedigree with an *FBN1* mutation causing non-syndromic ectopia lentis (NSEL) with retinal detachment (RD).

• **METHODS:** Eight affected individuals had pars plana vitreolensectomy for bilateral ectopia lentis (EL). Twelve eyes of 6 patients had secondary iris-claw intraocular lenses inserted and 4 eyes of 2 patients were managed with contact lenses. Rhegmatogenous retinal detachment (RRD) was treated when necessary. Pre- and post-operative assessment included visual acuity, endothelial cell count and dilated fundal examination.

• **RESULTS:** Macula-on RRD was present in all individuals >18y, 64% (7/11 eyes) presenting post-vitreolensectomy with 57% having bilateral non-synchronous RRD. Surgical aphakia was managed with iris-fixated intraocular lenses (IOL group, $n=6$), or contact lenses (CL group, $n=2$). Visual acuity ≥ 0.3 logMAR (driving standard) was achieved in 75% of IOL group eyes and 25% of the CL group eyes. Mean loss of corneal endothelial cell count in the IOL group was 4% at 2y post-operative.

• **CONCLUSION:** In this cohort, refractive management with iris-claw IOLs provided superior outcomes to contact lenses and the authors recommend this as the optimal refractive correction in EL patients.

• **KEYWORDS:** *FBN1*; isolated ectopia lentis; retinal detachment; iris-claw intraocular lenses

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INTRODUCTION

Inherited ectopia lentis (EL) may be dominant (*FBN1*, chromosome 15q21.1, OMIM *134797) or recessive (e.g. ADAMTSL4, OMIM*610113; ADAMTS10, OMIM*608990; ADAMTS17, OMIM*607511)^[1-2] and associated with a systemic features [syndromic EL (SEL)] or isolated [non-syndromic EL (NSEL)]. Disease severity and syndromic manifestation varies depending on the positioning and extent of deleteriousness associated with the causative mutation within the *FBN1* gene.

The final common pathway for EL is zonular breakdown leading to subluxation of the crystalline lens^[3]. Critical components of the ciliary zonules include the fibrillin protein^[4], ADAMTS superfamily proteins^[5], and collagens^[6]. Mutant fibrillin degrades more rapidly than the wild type variant^[5,7-8]. This may be related to TGF- β -mediated inflammation and elastolysis^[9].

The authors feel the term 'isolated EL' is a misnomer as it downplays the significance of the other blinding ocular features of NSEL, including axial myopia, rhegmatogenous retinal detachment (RRD), glaucoma, corneal flattening and astigmatism. NSEL can cause substantial ocular morbidity despite the lack of systemic mortality risk. Delayed detection of significant EL-related refractive error may cause amblyopia in up to 50%, which may be bilateral^[10-12]. The other ocular features of EL may be progressive and lead to acquired visual loss (e.g. glaucoma, RRD)^[9].

The genetic features of fibrillin-1 mutations have been described by this groups previously^[13]. There are numerous forms of SEL including Marfan Syndrome (MFS, OMIM#154700), Weill-Marchesani Syndrome (WMS) types 1-4 (OMIM #277600/#608328/#614819/#613195), and homocysteinuria (HCU, OMIM#236250). SEL often includes life threatening features. EL may be a useful clinical clue for investigation and management (*i.e.* aortic dissection in MFS^[14], and arteriovenous thrombosis in HCU^[15]). Presentation with poor vision often occurs early in both MFS and NSEL^[2] allowing detection of both familial and sporadic cases, facilitating instigation of potentially life-saving systemic investigations and treatment. Diagnostic criteria including clinical and genetic features have been proposed for MFS^[16] and biochemical and clinical tests for HCU^[17-18].

Table 1 Comparative analysis of features of *FBNI*-mediated disease

First author	Year	Country	Phenotype	Study type	<i>n</i>	EL	B/L EL	RRD	B/L RRD	Recurrent RRD	RRD post-VLE	AL (mm)
Stephenson ^[13]	2019	Ireland	NSEL	Retrospective	7	100%	100%	100%	57%	9%	64%	26.66
Chandra ^[23]	2014	UK	MFS	Survey	185	32%	75%	15.10%	44%	46%	21%	-
Maumenee ^[10]	1981	USA	MFS	Retrospective	160	60%	-	10%	23.08%	-	31.25%	25.96
Nemet ^[9]	2006	USA	MFS	Review	-	50%-87%	Usual	5%-25.6%	30%-42%	11%-25%	-	28
Konradsen ^[11]	2013	Sweden	MFS	Cohort	51	54%	29%	5.88%	1.96%	-	-	24.73
Schrijver ^[25]	1999	USA	MFS	Retrospective	25	86%	100%	23%	-	-	-	-
Manning ^[26]	2016	Ireland	MFS	Retrospective	15	100%	100%	0	-	-	-	-
Rabie ^[24]	2017	Iran	MFS	Prospective	9	100%	33%	8%	0	0	100%	26.24

EL: Percentage of cases with ectopia lentis; B/L EL: Of cases of EL, the percent of which were bilateral; RRD: Percentage of patients with at least one eye rhegmatogenous retinal detachment; B/L RRD: Of patients with RRD, percentage which were bilateral; Recurrent RRD: Of cases of RRD, percentage which experienced re-detachment; RRD post-VLE: Percentage of patients where RRD occurred after vitreolensectomy; AL: Axial length; -: Not available in the specified publications.

SUBJECTS AND METHODS

Ethical Approval Patients with a phenotype of EL were recruited to the vitreoretinopathy subgroup of Target 5000^[19-21]. All participants completed written informed consent. This study was approved by the institutional review board of the Mater Misericordiae and Mater Private Hospitals, Dublin, Ireland and abides by the Declaration of Helsinki.

Recruited patients underwent a detailed history and dilated ophthalmic examination. The pedigree was mapped in detail for 5 generations and available relatives were invited to participate. Retrospective review of any ophthalmic surgical procedures was carried out in the Mater Hospitals and in other units/jurisdictions. Multimodal retinal imaging was captured (widefield colour and autofluorescence, Optos plc, Scotland & Spectral Domain Optical Coherence Tomography (SD-OCT, Carl Zeiss Meditec, Germany). EL was surgically managed when conservative refractive measures no longer attained visual acuity sufficient to achieve the legal driving standard^[22]. Twelve eyes of six patients had secondary iris-fixated anterior chamber lenses inserted (Artisan Aphakia, Ophtec BV, Netherlands; IOL group). Refractive correction for four eyes of a further two affected family members were managed with contact lenses (CL group). Endothelial cell count (ECC) was measured pre- and post-operatively (Konan Non-Con Specular Microscope, NSP-9900, Konan Medical USA, Inc.) for all 12 eyes with surgical refractive correction. Best corrected visual acuity (BCVA) was recorded for all individuals. All data was recorded for retrospective analysis in a non-randomised, non-masked fashion. Genotyping was performed as detailed in a prior publication^[13].

As this study was a retrospective observational cohort study, no comparative statistical analyses were used, but a descriptive statistical assessment was employed.

RESULTS

Eight affected (mean age 53.38±19.94y) and two unaffected

(mean age 56.50±0.71y) adults from 3 generations of a single *FBNI* pedigree with NSEL were recruited. All affected individuals had bilateral EL and axial myopia (mean axial length 26.55±1.19mm, data available for 12 of 16 eyes).

RRD was present in all probands >18y with mean age at presentation of 40y (range 21-50y). Presentation was early with macula on RRD in all cases as the family had been educated regarding relevant symptoms and advised to present rapidly to the treating vitreoretinal (VR) surgeon. RRD occurred pre-lensectomy in 36% (4/11 eyes), all of which were operated on by a retired VR surgeon in another jurisdiction. Although operation notes are unavailable for these cases, patients report that their lensectomy was performed at the same procedure. Post-lensectomy RRDs were managed by pars plana vitrectomy/endolaser/C₂F₆ 18% gas tamponade in 50% of cases and scleral buckle with cryotherapy in 50%.

Mean BCVA was 0.18±0.21 and 1.60±1.82 logMAR for the IOL and CL groups respectively (*P*=0.01). Legal driving vision (≥0.3 logMAR^[22]) was maintained in 75% of eyes (all individuals) in the IOL group versus 25% of eyes (50% of individuals, *n*=1 of 2) in the CL group. One eye in the CL group had a poor visual outcome secondary to corneal scar due to microbial keratitis (MK) from prolonged contact lens wear. In the IOL group, ECC loss at 2y post-implantation was 4% (preop. 3093.50±161.14; 2y 2968.67±187.37). There was no compromise of endothelial function nor corneal clarity. This change in ECC was not statistically significant (*P*=0.09).

As previously reported, RRD was diagnosed in 78% of eyes over 18y^[13]. The rate of RRD in the current cohort is significantly higher than the reported rate of RRD associated with EL (0 to 25%, Table 1)^[9-11,13,23-26]. Disparity in visual acuity between eyes with prior RRD and never-detached eyes was not statistically significant (*P*=0.69) as all cases presented with macula on RRD, likely due to education regarding the high risk of RRD in their family and the value of early treatment.

Genetic findings are described in a previous paper^[13] with the NM_000138: c.1916G>A, p.Cys639Tyr variant detected in all affected individuals for the pedigree described herein. None of these patients meet the revised Ghent Criteria for MFS and importantly did not manifest any aortic signs or symptoms throughout their lives either clinically or echocardiographically.

DISCUSSION

Vitreolensectomy may be indicated in the 1st decade of life if EL/aphakia leads to conservatively non-correctible acuity^[27]. Thus, an appropriate choice of refractive correction warrants careful consideration. In EL, correction of progressive myopic astigmatism *via* conservative means (*i.e.* contact lens) has long been the mainstay of treatment^[28]. When adequate visual acuity was no longer feasible due to progressive crystalline lens subluxation, surgical intervention was warranted (*i.e.* pars plana vitreolensectomy with secondary iris-fixated IOL). In this cohort, driving visual acuity was maintained in all patients treated with iris-fixated lenses with no anterior segment adverse effects. There is contention surrounding the use of iris-fixated lenses in young patients concerning endothelial cell loss^[29]. However, several large multicentre prospective studies showed minimal or no loss of ECC when iris-fixated IOLs were used in phakic^[30] and aphakic^[31] eyes. ECC loss is more likely when EL was acquired due to trauma and this is most likely due to the inciting trauma rather than the IOL choice^[32]. We maintain that the benefit of stable, optimal refractive correction in preventing amblyopia in children counteracts this potential risk to the corneal ECC as also suggested by others^[26,33-35]. In a retrospective case-control series, ECC was not found to be statistically significantly less than fellow eyes which underwent uncomplicated phacoemulsification with in-the-bag intraocular lens implantation^[36]. Although traditional anterior chamber intraocular lenses (ACIOLs) are an option in the management of aphakia, these are poorly studied in the younger age group described here. The long-term effects of an angle-supported ACIOL on both the corneal endothelium and iridocorneal angle as well as their centration are a matter of concern in EL eyes, considering the deep anterior chambers and large white-to-white measurements from lax ciliary muscles^[37-38]. Posterior chamber scleral-fixated IOLs are another option for the refractive correction of aphakia after vitreolensectomy; however, this procedure is more technically demanding and holds the risk of late lens dislocation (circa 10y) into the vitreous cavity due to suture rupture^[39].

The patient reported here with poor vision due to corneal scar was managing their aphakic refractive correction with contact lenses. She developed MK with an advanced central corneal scar in that eye. The rate of MK from contact lens wear ranges from 1.9 to 25 per 10 000^[40]. In comparison, the safety parameters from the iris-fixated IOL group show no corneal-

related visual loss at 2y post iris-fixated IOL implantation.

Although the cohort described here are young adults, iris-fixated IOLs have provided stable refractive correction with no adverse corneal changes. The authors note that the outcomes from the CL group are biased due to small sample size; however, in this case visual loss due to MK/corneal scar occurred in one eye (25%, $n=1/4$) after 10y of CL correction. The authors recommend iris-fixated IOL as the primary method of aphakic refractive correction when surgical intervention is warranted. This minimises risk of MK and negates CL compliance issues in children. The timing of surgical intervention should be dictated by the inability to counteract progressive astigmatism due to EL by conservative means and not prohibited by concern regarding the risks of iris-fixated lens implantation. Lensectomy may need to be performed on an emergent basis in the presence of RRD to facilitate visualisation and treatment of peripheral retinal breaks. A lower threshold to intervene surgically in young children with significant anisometropia should be maintained. Further studies with longer-term data are required to make a definitive statement.

EL poses a diagnostic and therapeutic challenge for both ophthalmic and systemic disease. Early genetic diagnosis may allay concerns of developing systemic features as well as informing biochemical diagnosis and management. Surgical intervention (*i.e.* vitreolensectomy) should be instigated by the development of visually significant lens subluxation which is not correctable by conservative refractive means or acutely in the presence of RRD. In this single pedigree cohort with a pathogenic *FBN1* mutation, iris-fixated IOLs achieved ideal refractive correction with visual outcomes superior to CL correction despite prevalent RRD.

In conclusion, the surgical management of a single pedigree with non-syndromic EL with pars plana vitreolensectomy and iris-fixated IOLs gives superior visual and safety outcomes to contact lens refraction.

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REFERENCES

- 1 Chandra A, Aragon-Martin JA, Hughes K, Gati S, Reddy MA, Deshpande C, Cormack G, Child AH, Charteris DG, Arno G. A genotype-phenotype comparison of ADAMTSL4 and FBN1 in isolated ectopia lentis. *Invest Ophthalmol Vis Sci* 2012;53(8):4889-4896.
- 2 Li J, Jia XY, Li SQ, Fang SH, Guo XM. Mutation survey of candidate genes in 40 Chinese patients with congenital ectopia lentis. *Mol Vis* 2014;20:1017-1024.

- 3 Jones W, Rodriguez J, Bassnett S. Targeted deletion of fibrillin-1 in the mouse eye results in ectopia lentis and other ocular phenotypes associated with Marfan syndrome. *Dis Model Mech* 2019;12(1):dmm037283.
- 4 Sakai LY, Keene DR, Engvall E. Fibrillin, a new 350-kD glycoprotein, is a component of extracellular microfibrils. *J Cell Biol* 1986;103(6):2499-2509.
- 5 Hubmacher D, Apte SS. Genetic and functional linkage between ADAMTS superfamily proteins and fibrillin-1: a novel mechanism influencing microfibril assembly and function. *Cell Mol Life Sci* 2011;68(19):3137-3148.
- 6 De Maria A, Wilmarth PA, David LL, Bassnett S. Proteomic analysis of the bovine and human ciliary zonule. *Invest Ophthalmol Vis Sci* 2017;58(1):573-585.
- 7 Aoyama T, Francke U, Dietz HC, Furthmayr H. Quantitative differences in biosynthesis and extracellular deposition of fibrillin in cultured fibroblasts distinguish five groups of Marfan syndrome patients and suggest distinct pathogenetic mechanisms. *J Clin Invest* 1994;94(1):130-137.
- 8 Reinhardt DP, Ono RN, Notbohm H, Müller PK, Bächinger HP, Sakai LY. Mutations in calcium-binding epidermal growth factor modules render fibrillin-1 susceptible to proteolysis. A potential disease-causing mechanism in Marfan syndrome. *J Biol Chem* 2000;275(16):12339-12345.
- 9 Nemet AY, Assia EI, Apple DJ, Barequet IS. Current concepts of ocular manifestations in Marfan syndrome. *Surv Ophthalmol* 2006;51(6):561-575.
- 10 Maumenee IH. The eye in the Marfan syndrome. *Birth Defects Orig Artic Ser* 1982;18(6):515-524.
- 11 Konradsen TR, Zetterström C. A descriptive study of ocular characteristics in Marfan syndrome. *Acta Ophthalmol* 2013;91(8):751-755.
- 12 Romano PE, Kerr NC, Hope GM. Bilateral ametropic functional amblyopia in genetic ectopia lentis: its relation to the amount of subluxation, an indicator for early surgical management. *Binocul Vis Strabismus Q* 2002;17(3):235-241.
- 13 Stephenson KAJ, Dockery A, O'Keefe M, Green A, Farrar GJ, Keegan DJ. A FBN1 variant manifesting as non-syndromic ectopia lentis with retinal detachment: clinical and genetic characteristics. *Eye (Lond)* 2020;34(4):690-694.
- 14 Attias D, Stheneur C, Roy C, Collod-Bérout G, Detaint D, Faivre L, Delrue MA, Cohen L, Francannet C, Bérout C, Claustres M, Iserin F, Khau van Kien P, Lacombe D, Le Merrer M, Lyonnet S, Odent S, Plauchu H, Rio M, Rossi A, Sidi D, Steg PG, Ravaud P, Boileau C, Jondeau G. Comparison of clinical presentations and outcomes between patients with TGFBR2 and FBN1 mutations in Marfan syndrome and related disorders. *Circulation* 2009;120(25):2541-2549.
- 15 Mudd SH, Skovby F, Levy HL, Pettigrew KD, Wilcken B, Pyeritz RE, Andria G, Boers GH, Bromberg IL, Cerone R. The natural history of homocystinuria due to cystathionine beta-synthase deficiency. *Am J Hum Genet* 1985;37(1):1-31.
- 16 Loeyls BL, Dietz HC, Braverman AC, Callewaert BL, De Backer J, Devereux RB, Hilhorst-Hofstee Y, Jondeau G, Faivre L, Milewicz DM, Pyeritz RE, Sponseller PD, Wordworth P, De Paepe AM. The revised Ghent nosology for the Marfan syndrome. *J Med Genet* 2010;47(7):476-485.
- 17 Jakubowski H, Boers GH, Strauss KA. Mutations in cystathionine beta-synthase or methylenetetrahydrofolate reductase gene increase N-homocysteinylated protein levels in humans. *FASEB J* 2008;22(12):4071-4076.
- 18 Cappuccio G, Cozzolino C, Frisso G, Romanelli R, Parenti G, D'Amico A, Carotenuto B, Salvatore F, Del Giudice E. Pearls & oysters: familial epileptic encephalopathy due to methylenetetrahydrofolate reductase deficiency. *Neurology* 2014;83(3):e41-e44.
- 19 Dockery A, Stephenson K, Keegan D, Wynne N, Silvestri G, Humphries P, Kenna PF, Carrigan M, Farrar GJ. Target 5000: target capture sequencing for inherited retinal degenerations. *Genes (Basel)* 2017;8(11):E304.
- 20 Carrigan M, Duignan E, Malone CP, Stephenson K, Saad T, McDermott C, Green A, Keegan D, Humphries P, Kenna PF, Farrar GJ. Panel-based population next-generation sequencing for inherited retinal degenerations. *Sci Rep* 2016;6:33248.
- 21 Farrar GJ, Carrigan M, Dockery A, Millington-Ward S, Palfi A, Chadderton N, Humphries M, Kiang AS, Kenna PF, Humphries P. Toward an elucidation of the molecular genetics of inherited retinal degenerations. *Hum Mol Genet* 2017;26(R1):R2-R11.
- 22 Irish Road Safety Authority. *Medical Aspects of Driver Licensing: A Guide for Registered Medical Practitioners 2010*. https://www.rsa.ie/Documents/Licensed%20Drivers/Guidelines_Medical_Fitness_toDrive1.pdf. Accessed on: 10/09/2019.
- 23 Chandra A, Ekwalla V, Child A, Charteris D. Prevalence of ectopia lentis and retinal detachment in Marfan syndrome. *Acta Ophthalmol* 2014;92(1):e82-e83.
- 24 Rabie HM, Malekifar P, Javadi MA, Roshandel D, Esfandiari H. Visual outcomes after lensectomy and iris claw artisan intraocular lens implantation in patients with Marfan syndrome. *Int Ophthalmol* 2017;37(4):1025-1030.
- 25 Schrijver I, Liu W, Brenn T, Furthmayr H, Francke U. Cysteine substitutions in epidermal growth factor-like domains of fibrillin-1: distinct effects on biochemical and clinical phenotypes. *Am J Hum Genet* 1999;65(4):1007-1020.
- 26 Manning S, Lanigan B, O'Keefe M. Outcomes after lensectomy for children with Marfan syndrome. *J AAPOS* 2016;20(3):247-251.
- 27 Zadeh N, Bernstein JA, Niemi AK, Dugan S, Kwan A, Liang D, Hyland JC, Hoyme HE, Hudgins L, Manning MA. Ectopia lentis as the presenting and primary feature in Marfan syndrome. *Am J Med Genet A* 2011;155A(11):2661-2668.
- 28 Neely DE, Plager DA. Management of ectopia lentis in children. *Ophthalmol Clin North Am* 2001;14(3):493-499.
- 29 Barbara R, Rufai SR, Tan N, Self JE. Is an iris claw IOL a good option for correcting surgically induced aphakia in children? A review of the literature and illustrative case study. *Eye (Lond)* 2016;30(9):1155-1159.

- 30 Silva RA, Jain A, Manche EE. Prospective long-term evaluation of the efficacy, safety, and stability of the phakic intraocular lens for high myopia. *Arch Ophthalmol* 2008;126(6):775-781.
- 31 Aspiotis M, Asproudis I, Stefanidou M, Gorezis S, Psilas K. Artisan aphakic intraocular lens implantation in cases of subluxated crystalline lenses due to Marfan syndrome. *J Refract Surg* 2006;22(1):99-101.
- 32 Kodjikian L, Beby F, Spire M, Gambrelle J, Hubert I, Burillon C, Grange JD, Garweg JG. Combined pars Plana phacofragmentation, vitrectomy, and Artisan lens implantation for traumatic subluxated cataracts. *Retina* 2006;26(8):909-916.
- 33 Siganos DS, Siganos CS, Popescu CN, Margaritis VN. Clear lens extraction and intraocular lens implantation in Marfan's syndrome. *J Cataract Refract Surg* 2000;26(5):781-784.
- 34 Català-Mora J, Cuadras D, Díaz-Cascajosa J, Castany-Aregall M, Prat-Bartomeu J, García-Arumí J. Anterior iris-claw intraocular lens implantation for the management of nontraumatic ectopia lentis: long-term outcomes in a paediatric cohort. *Acta Ophthalmol* 2017;95(2):170-174.
- 35 Cleary C, Lanigan B, O'Keeffe M. Artisan iris-claw lenses for the correction of aphakia in children following lensectomy for ectopia lentis. *Br J Ophthalmol* 2012;96(3):419-421.
- 36 Güell JL, Verdager P, Mateu-Figueras G, Elies D, Gris O, Amich JM, Manero F, Morral M. Unilateral iris-claw intraocular lens implantation for aphakia: a paired-eye comparison. *Cornea* 2016;35(10):1326-1332.
- 37 Por YM, Lavin MJ. Techniques of intraocular lens suspension in the absence of capsular/zonular support. *Surv Ophthalmol* 2005;50(5):429-462.
- 38 Ellerton CR, Rattigan SM, Chapman FM, Chitkara DK, Smerdon DL. Secondary implantation of open-loop, flexible, anterior chamber intraocular lenses. *J Cataract Refract Surg* 1996;22(7):951-954.
- 39 Price MO, Price FWJr, Werner L, Berlie C, Mamalis N. Late dislocation of scleral-sutured posterior chamber intraocular lenses. *J Cataract Refract Surg* 2005;31(7):1320-1326.
- 40 Stapleton F, Carnt N. Contact lens-related microbial keratitis: how have epidemiology and genetics helped us with pathogenesis and prophylaxis. *Eye (Lond)* 2012;26(2):185-193.