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Management Strategies of Ocular Abnormalities in Patients with Marfan Syndrome: Current Perspective

Hamed Esfandiari [1,2], MD; Shabnam Ansari[1], MD. Hossein Mohammad Rabie[1]

1 Ophthalmic Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2 Department of Ophthalmology, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.

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Correspondence to: Shabnam Ansari, MD
Department of Ophthalmology, Labbafinejad Medical Center, Boostan 9 St., Pasdaran Ave., Tehran 16666-94516, Iran;
Email: Sh.ansari@gmail.com

Running Title: management of ocular abnormalities in Marfan syndrome

Abstract

Marfan syndrome is an autosomal dominant genetic connective tissue disorder that results from mutations in the fibrillin-1 gene located on chromosome band 15q 15–21. Fibrillin, a glycoprotein, is widely expressed throughout the body and contribute to elasticity and force-bearing capacity of connective tissue. In the eye, fibrillin is a key constituent of the ciliary zonules, which suspend the crystalline lens in place. The zonular defect leads to ectopia lentis that is hallmark of Marfan ocular abnormalities and occurs in 60 to 80% of cases. Other less common ocular features of Marfan syndrome are increased axial length, astigmatism, and flat cornea. Visual function in Marfan syndrome could be affected in several ways: ectopia lentis, refractive error, amblyopia, retinal detachment, cataract, and glaucoma. Management of subluxated lens starts with correction of refractive error with eyeglasses in mild cases. In more severe cases, especially when lens bisects the pupil, complete correction of refractive error is impossible without removing subluxated lens. The best method for visual rehabilitation after lens extraction is still debated. Aphakic Artisan implantation at the time of subluxated lens removal results in good visual outcomes with acceptable safety profile. Studies with longer term follow up and larger sample populations are needed to evaluate the safety of this procedure in patients with Marfan syndrome.

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Introduction

Marfan syndrome is an autosomal dominant disease that is characterized by musculoskeletal abnormalities, cardiovascular disease, and ocular abnormalities. It is a disorder of connective tissue protein fibrillin-1 and transforming growth factor-beta (TGF-beta) that lead to abnormal connective tissue in many organs. [1]

It is important to diagnose patients with Marfan syndrome accurately. Ghent nosology is the well established diagnostic criterion for Marfan syndrom. [2] The Ghent criteria are divided into seven areas: cardiovascular system, ocular system, skeletal system, dura mater, pulmonary system, skin and integument, and family or genetic history. The major ocular criterion is ectopia lentis and the minor ocular criteria include abnormally flat cornea, increased axial length of the globe, and hypoplastic iris or hypoplastic ciliary muscle causing anisocoria. Since 2010, ectopis lentis is considered a cardinal clinical feature of Marfan syndrome, which differentiates Marfan syndrome with more sensitivity and specificity. [3, 4]

Fibrillin is distributed throughout ocular tissues, so Marfan syndrome can affect different parts of the eye. [5] (Table 1)

Almost 50% of patients are diagnosed by Marfan syndrome primarily as part of the evaluation for ophthalmic complaints.[6] Common causes of visual abnormalities in patients with the Marfan syndrome are ectopia lentis, refractive error, amblyopia, retinal detachment, cataract, and glaucoma. This present review will give a brief overview of ocular features of the Marfan syndrome and discuss current management.

Table 1- Ocular abnormalities in Marfan syndrome:

Antrior segment	Cornea	Flattened Corneas and Astigmatism Megalocornea
	Angle	Glaucoma
	Iris	Poor dilated pupil Iris coloboma
	Lens abnormalities	Ectopia lentis Microspherophakia Lens opacity Lens coloboma
Posterior segment	Vitreous	Liquefaction Abnormal vitreous attachments along the lattice degenerations
	Retina	Retinal degeneration Retinal tears

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	Retinal detachment
Choroid	Thin choroid
Sclera	Thin sclera
Globe	Long axial length strabismus

Ectopia lentis

Ectopia lentis or lens subluxation is the predominant ocular complication of Marfan syndrome. [7] The incidence of ectopia lentis in Marfan syndrome varies from 50% to 72% in different studies and tends to occur in the fourth and fifth decade of life.[8,9] [10,11] [12] Zonules suspend the crystalline lens behind the iris and they are made of fibrillin. Fibrillin abnormalities in Marfan syndrome lead to zonular weakness and subluxation of the lens. Subluxation is usually toward superior and temporal, although dislocation into the vitreous or anterior chamber may also occur. [13]

This abnormality may present with symptoms like blurred vision, fluctuating vision, and monocular diplopia. Ocular examination may show lens subluxation, dislocation, iridodonesis and irregular astigmatism.[5,14]

Eyeglasses are the first step to correct blurred vision caused by subluxated lenses.[5] Prescribing the glasses in Marfan patients with the subluxated lens is challenging.[15] In mild cases correcting myopic astigmatism is all that patients need. If subluxated lens splits the pupil, correcting the aphakic part leads to a better outcome as images are less distorted by lenticular astigmatism. Ophthalmologists should decide whether aphakic or phakic pupil must be corrected. In the case of mild subluxation, patient sees through crystalline lens and lenticular astigmatism should be corrected. But with significant lens subluxation, clear view through the lens is impossible and aphakic eyeglasses should be prescribed. [16]

Depending on the patients' age, preference, job and other conditions, contact lenses can be used as an alternative.

In the past, because of the high rate of intra and postoperative complications and poor visual outcome in Marfan syndrome, surgery was not a popular option. [17] Nowadays with the advance in microsurgical instruments and operation techniques, surgery has gained interest to improve visual function.

Lens extraction is the main type of treatment for anterior lens dislocation.

The indications for surgery in lens dislocation are: inability to achieve good corrected visual acuity, risk of amblyopia in children, posterior dislocation of the lens into vitreous cavity, anterior dislocation of the lens +/- secondary glaucoma, impending to complete dislocation, and lens-induced glaucoma or uveitis, cataract.

Subluxated Lens extraction in these patients is challenging. The weakness of zonular and lens instability is frequently complicated by the loss of capsular bag, vitreous disturbance, and endothelial cell damage.

Forty eyes of patients with Marfan's syndrome who underwent pars plana vitreolensectomy for subluxated lenses were evaluated. No patients in this series suffered a reduction in visual acuity as a result of surgical intervention, with a mean improvement of 2.8 lines Snellen acuity. The surgery had acceptable complication rate and postoperative incidence of retinal detachment was 6%. [18]

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Within-the-bag lensectomy combined with a limited anterior vitrectomy is a safe procedure in children with lens subluxation. Anteby et al followed 22 cases of the Marfan syndrome with subluxated lens who underwent within the bag lensectomy for 6 ± 4.6 years and demonstrated stable visual acuity with minor fluctuations as well as normal intraocular pressure in all cases.[17] Only one case developed retinal detachment 4 years after the surgery, which emphasizes the importance of long-term follow-up in these cases.

Although lens extraction is considered a safe and effective method to remove subluxated or dislocated lens, retinal detachment is a possible complication in Marfan syndrome. [19,20,21,22]

Visual rehabilitation after lens extraction is an unresolved dilemma. Aphakic glasses are the safest method to correct aphakia and provide a consistent visual outcome in patients. Especially, it is important in pediatric patients, in whom follow-up for artificial intraocular lenses is limited.[21].[23]

Lens extraction combines with artificial intraocular lens replacement is another choice of surgery for the Marfan syndrome. [24] Options for intraocular lens include an anterior chamber intraocular lens (ACIOL), posterior chamber intraocular lens (PCIOL) fixed to the sclera and/or to the iris, and scleral-fixated capsular tension rings.

Not long ago flexible open-loop ACIOL implantation was the most commonly used method for aphakic correction. Pars plana lensectomy with primary ACIOL implantation in both children and adults with Marfan syndrome demonstrated good postoperative corrected visual acuity and no serious complication in short-term follow-up. [25] [26]

But there are concerns regarding this practice in Marfan syndrome. The anterior chamber is excessively deep in most Marfan cases which prevent appropriate fitting of IOL and leads to exaggerated IOL movement. Loose fit causes pigment release, glaucoma, corneal decompensation, and inflammation.

Considering these complications, PCIOLs seem to be a better option as it is not positioned in the anterior chamber and the size is bigger than ACIOL. PCIOL implantation in these cases is technically demanding and needs more time. Scleral fixation of PCIOLs in children without adequate capsular support can be visually rewarding in selected cases, but there is a high rate of complications during long-term follow-up. [27]

Sulcus fixation of an IOL in eyes without capsular support is an option to correct aphakia in children. [28] In their study, Zetterstrom et al implanted the IOL into the sulcus and sutured the haptics of IOL to scleral bed. They followed their cases for 9 to 33 months and no opacification of the visual axis, secondary glaucoma, or retinal complication was reported during follow-up.

Aspiotis et al performed lens extraction and Artisan (iris claw ACIOL) IOL implantation in 2 children and 3 adults with lens subluxation due to Marfan syndrome. [29,30] In their report BCVA improved 4 Snellen lines and endothelial cell counts remained constant during 6 months follow up. Following this study, Samina et al presented two patients with the Marfan syndrome who underwent lens extraction and Artisan implantation that were followed for 12 years. This long-term follow up showed good visual outcome and no serious IOL related complication. [31] Endothelial cell counts were within expected range for their age at final follow up visit.

In another cases series, Rabie et al evaluated the outcome of lens extraction and Artisan implantation in 12 eyes of 9 patients with the Marfan syndrome. Only one case of retinal detachment 2 months after the surgery and one case of IOL subluxation were reported in this series during 44.5 months follow up [32]

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The main concern regarding Artisan fixation is endothelial cell loss. Because of their retrospective nature, none of the previous studies evaluated the endothelial cell count before and after IOL implantation. Other studies compared the cell counts with aged-matched population and reported no significant difference. [29,31]

In a randomized clinical trial, endothelial cell loss in iris fixated IOL group was 19.3% at one year follow up which was comparable to sclera fixation group. [33]

In attempt to save cornea from possible IOL induced damages, retropupillary iris-claw IOL fixation is also used to correct aphakia in these cases. [34]

Few studies in the literature compared different type of IOL implantation in Marfan syndrome. [35,33] In a randomized clinical trial Zheng et al compared clinical outcomes of iris-fixated ACIOL and scleral-fixated PCIOL in seventy-one eyes of 49 patients with Marfan syndrome and lens subluxation. While endothelial cell loss was comparable between 2 groups, complications were significantly higher in sclera fixation group and almost 50% of cases developed IOL decentration. [33]

Another option to stabilize the capsular bag is to use capsular tension ring (CTR). Nonetheless, CTR cannot correct decentration and since the zonular weakness in Marfan syndrome is progressive, both IOL and CTR are subject to further decentration or even dislocation. [36]

To overcome this obstacle, Bahar et al used Cionni ring and sutured it to the sclera in 12 eyes of 9 patients with the Marfan syndrome. IOL centration was excellent during follow up but 3 patients developed posterior capsule opacification. [15,37,38]

IOL power calculation is also an important issue in patients with the Marfan syndrome. They usually have longer axial length and the staphylomatous area in posterior pole that can lead to axial length miscalculation with ultrasound biometry. If the ultrasound hit the staphyloma, the calculated power of IOL results in underestimation and hyperopia after surgery.[35,39]

Refractive error

Most of the patients with the Marfan syndrome have myopia due to long axial length. Prevalence of myopia in Marfan syndrome (34%-44%0) is more than the general population. [5,8,9] In one report more than 50% of patients with the Marfan syndrome have myopia of -3.00 or more. [41] They may also suffer from lenticular astigmatism due to lens subluxation. Kinori et al showed increased corneal astigmatism in addition to lenticular astigmatism. [42]

Refractive error can be corrected with glasses or contact lenses (special flat contacts may be required for proper correction).

Corneal refractive surgery (laser keratotomy) is not recommended for most patients with Marfan syndrome as the cornea is markedly flat in these cases.

Mild cases of myopia can be corrected with laser surgery in people with Marfan syndrome if they do not have lens dislocation. In the presence of lens subluxation, laser ablation is not recommended because it may make the dislocation worse in case of LASIK surgery, and also interfere with detailed IOL calculation for future IOL implantation.

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Amblyopia

Children with the Marfan syndrome are at risk of amblyopia. Ocular abnormalities such as myopia, astigmatism, anisometropia, ectopia lentis, and retinal pathologies may result in amblyopia.
Romano et al evaluated the visual outcome of conservative (non- surgical) therapy in patients with hereditary ectopia lentis. Almost half of the cases developed significant permanent functional amblyopia (visual acuity 20/50 to 20/200) in spite of good conservative management. The worst amblyopia occurred when the lens was still covering the visual axis and the lens edge was 1.3 mm from the center of the pupil (range of 0.3 to 2.3 mm). Based on this study early surgical intervention in children with lens subluxation who are nonresponsive to conservative management should be considered. [43]

Retinal disease

Posterior segment pathology is present in 18% of eyes in the Marfan syndrome and incidence is even higher (70%) in patients with a subluxed lens.[44] The incidence of retinal detachment in Marfan syndrome ranges from 5% to 25.6%.[21,45,46]
Predisposing factors for retinal breaks in Marfan syndrome include ectopia lentis, long axial length, vitreous liquefaction and posterior vitreous detachment without any dehiscence at the vitreoretinal interface, and abnormal vitreoretinal adhesions. Risk factors for retinal detachment in Marfan syndrome include younger age, ectopia lentis, history of lensectomy and aphakia. [5,22,45,47,48]
Because of the risk of retinal detachment, people with Marfan syndrome should have complete ophthalmic exam routinely once a year and anytime they have any ophthalmic complaint. In case of limited cooperation, young age and ocular abnormalities such as miotic pupil, ophthalmologist can use widefield retinal image to complete the retinal exam.[44]
Treatment in most cases is surgical intervention and it should be performed as soon as possible. Retinal detachment surgery in Marfan syndrome is challenging because of ocular abnormalities such as thin sclera, miotic pupils, and multiple breaks.[14] In the past, surgeries for retinal detachment in Marfan syndrome had less favorable outcome than retinal detachment in the normal population. Nowadays, with modern surgical techniques and instrumentation, outcome of retinal surgery is comparable between patients with Marfan syndrome and normal population. Currently available vitreoretinal surgical techniques result in successful reattachment of the retina in approximately 86% of the eyes.[45,46] Failure of surgery in Marfan syndrome is due to proliferative retinopathy and poor visualization of retinal periphery. [22,47,49]

Two surgical procedures for retinal detachment repair are scleral buckling and vitreous surgery. Scleral buckling is the first choice if there is clear normal lens, clear subluxated lens without any interference with fundus details, and retinal breaks being at or anterior to the equator
Otherwise, vitreoretinal surgery should be performed. Prognosis depends on the location and extent of the detachment, the time interval between symptoms start and surgery, and phakic or aphakia condition. [50]

Retinal detachment in patients with Marfan syndrome tends to occur bilaterally (30-42%). It is important to carefully examine the fellow eye and do preventive barrier laser if necessary. [47-49]

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Cataract

Although the prevalence of cataract doesn't seem to be higher in Marfan syndrome, it tends to occurs earlier at younger age. Posterior subcapsular cataract and localized globular lens opacities are common type of cataract in Marfan syndrome. [10]

As zonular weakness renders the eye susceptible to surgical complications, surgery should be performed by experienced surgeon in well equipped operation room. Intra operation complications include vitreous loss, rupture of the residual zonules, and extension of the capsulotomy. Post operation complications include Vitreous incarceration in the wound, iris prolapse, corneal edema, postoperative hyphema, and persistent postoperative iritis.[10]

Glaucoma

About one-third of patients with the Marfan syndrome will develop glaucoma sometimes in their life. [14] Usually, in these cases, glaucoma is diagnosed at a younger age.

Most common type of glaucoma in Marfan syndrome is primary open-angle glaucoma. While primary angle closure glaucoma has not been reported in this condition, pupilary block mechanism can rarely happen due to anterior dislocation of the lens. [5,13] Although not as common as in hemochromatosis, anterior lens dislocation may happen spontaneously or secondary to trauma. [13,41] In this situation lensectomy is definite treatment.

The possible mechanism for open angle glaucoma is the abnormal insertion of the ciliary musculature into the trabecular meshwork and displacement of Schlemms' cannal.[51]

Secondary open angle glaucoma may occur due to retinal detachment, vitreoretinal or lens extraction surgerie, iritis, or pigment dispersion due to excessive movement of PCIOL.[51]

Management of glaucoma starts with antiglaucoma medications. If the patients use a systemic beta blocker for cardiovascular abnormalities, topical beta blocker has minimal effect to lower the intraocular pressure.

Choice of glaucoma surgery in patients with Marfan syndrome depends on the lens position. If the lens is normal, minimally invasive glaucoma surgeries or non-penetrating deep sclerotomy are preferred first line interventions. These eyess are more susceptible to hypotony-related complications of incisional surgeries, and there is a risk of further lens subluxation in postoperative fluctuating anterior chamber. [52]

Conclusion:

Ophthalmologists play a substantial role in detecting Marfan syndrome. The diagnosis and management of the associated eye conditions are challenging. Patients should be evaluated by ophthalmologist for refraction, IOP, lens status, peripheral retina and changes in optic nerve.

In case of lens subluxation, the first line of management is correcting the refractive error with eyeglasses. If lens is bisecting the pupil, eyeglasses alone are unlikely to correct the visual function, and removal of crystalline lens is necessary. In most cases aphakic Artisan IOL is safe and effective means for visual rehabilitation. After the surgery patients should be routinely followed for IOL centration and retinal periphery. Patients should also be advised to seek instant ophthalmological consultation if they see flashes

and floaters, or experience any partial or complete loss of visual acuity. Timely intervention for retinal detachment can preserve patients' visual function.

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