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Title: Surgical and Visual Outcomes of the Type I Boston Keratoprosthesis for the Management of Aniridic Fibrosis Syndrome in Congenital Aniridia

Authors:

Pejman Bakhtiari, Illinois Eye and Ear Infirmary, University of Illinois at Chicago
Clara Chan, Cincinnati Eye Institute, University of Cincinnati, Cincinnati, Ohio
Jeffrey D. Welder, Illinois Eye and Ear Infirmary, University of Illinois at Chicago
Jose De La Cruz, Illinois Eye and Ear Infirmary, University of Illinois at Chicago
Edward J. Holland, Cincinnati Eye Institute, University of Cincinnati, Cincinnati, Ohio
Ali R. Djalilian, Illinois Eye and Ear Infirmary, University of Illinois at Chicago

Corresponding Author:

Ali R. Djalilian, M.D.
Assistant Professor of Ophthalmology
adjalili@uic.edu
312-996-8937 (phone)
312-355-4248 (fax)
Department of Ophthalmology and Visual Sciences
University of Illinois at Chicago
1855 W. Taylor Street M/C 648
Chicago, IL 60612

Institutional affiliation (in addition to above):

1945 CEI Drive
Cincinnati, OH 45242

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Short Title: Boston Keratoprosthesis for Aniridia Fibrosis Syndrome

Introduction

Congenital aniridia is a panocular disease traditionally described as the classic triad of aniridia, foveal hypoplasia and nystagmus¹. We now know that congenital aniridia is a spectrum of diseases resulting from mutations or deletions in *PAX6*, the master control gene for eye development on chromosome 11p13.² Congenital aniridia affects a variety of ocular structures including the cornea, anterior chamber, iris, lens, macula and optic nerve.³ While foveal hypoplasia remains the major factor limiting visual acuity, many experience decline visual acuity from the development of a presenile cataract (50-85%)³, glaucoma (50-75%)⁴, and aniridic keratopathy (20%).⁵

Management of congenital aniridia usually begins medically, however eventually all patients will need several surgical interventions to preserve or restore their baseline visual acuity⁵. Implantation of intraocular lens (IOL) and tube shunts to control glaucoma are common. In addition, many will require limbal stem cell and corneal transplantation for aniridic keratopathy.⁵

The corneal changes associated with aniridic keratopathy include vascular pannus formation, conjunctivalization, epithelial erosions, and subepithelial fibrosis.⁸ These corneal changes are primarily due to progressive limbal stem cell deficiency.⁹ Ocular surface reconstruction with limbal stem cell transplantation, either with or without corneal transplantation, provide long-term favorable outcomes in aniridic keratopathy by restoring limbal stem cell function.⁹ The use of the Type 1 Boston Keratoprosthesis (Boston Kpro) is a novel approach to manage aniridic keratopathy with favorable outcomes in terms of visual acuity and device retention. Additionally, keratoprosthesis eliminates the need for systemic immunosuppressive therapy required after limbal stem cell allograft.¹⁰

Tsai et al were the first to describe a postsurgical anterior chamber progressive fibrosis that occurred in patients with congenital aniridia who had undergone multiple intraocular surgeries.¹¹ They termed the disease *aniridic fibrosis syndrome*. Our study represents a case series on the syndrome and describes the clinical features and surgical outcomes in nine patients. In addition, we report the use of Type 1 Boston Kpro as a surgical option in this subset of aniridic patients.

Patients and Methods

A retrospective chart review of four eyes in four consecutive patients with congenital aniridia who developed aniridic fibrosis syndrome from March 2006 to December 2009 at the University of Illinois Eye and Ear Infirmary and five eyes in five patients at the Cincinnati Eye Institute from July 1999 to January 2010 were performed. Pertinent recorded data included age, sex, past ocular history

including medical and surgical interventions, Snellen visual acuity and clinical exam findings.

Surgical intervention included IOL explantation (7 cases) and removal of fibrosis with anterior vitrectomy (1 case) or pars plana vitrectomy (8 cases). In seven of nine eyes, a type I Boston Kpro was implanted primarily. One eye had a Boston Kpro prior to the development of fibrosis development which was later repeated because of a corneal melt. In the remaining case, an Alphacor Kpro (Argus Biomedical Pty Ltd., Perth, Australia) was exchanged for Boston Kpro. Boston Kpro (Massachusetts Eye and Ear Infirmary, Boston, MA) was used in all cases with PMMA backplate of 8.5 mm in diameter.

Results

Patient data and outcomes are presented in Table 1.

Representative Case Report:

Case 1: An 11 year old female with congenital aniridia was referred for a left corneal opacity and gradual decline in visual acuity over 3 months. Ocular history was significant for secondary glaucoma in both eyes with tube shunts placed 6 and 2 years ago in the right and left eyes, respectively. Family history was positive for aniridia. Visual acuity in the left eye was count fingers at 3 feet which had declined from 20/400. Intraocular pressure was 10 mmHg. The cornea was cloudy and edematous. Anterior and posterior chamber exam revealed a dense retrocorneal and retrolental membrane with anterior displacement of the PCIOL. Posterior exam was limited by corneal opacity and the anterior segment membrane. A diagnosis of aniridic fibrosis syndrome was made and the patient underwent IOL explantation and anterior vitrectomy. Post-operatively, visual acuity improved to 20/400. However, at 12 months the membrane recurred and visual acuity decreased to HM. On examination, the patient had significant corneal decompensation and anterior chamber fibrosis (Fig 1A). The patient then underwent pars plana vitrectomy, membrane removal, and implantation of a Boston Kpro. At 6 months after the Kpro surgery, a thin retrosprosthetic membrane was observed and successfully cleared by Yag laser, improving her visual acuity to 20/200 (Fig 1b).

Summary of findings:

All nine patients were diagnosed as congenital aniridia based on clinical features. One patient had WAGR syndrome. The patients ranged in age from 11-71 years (mean 33.8 years). All patients had previous cataract surgery with PCIOL implantation. Seven of the nine patients had existing tube shunts for glaucoma. Seven patients had previous corneal transplantation, seven had

previous keratolimbal allograft, one had an existing Boston Kpro, and one had existing Alphacor Kpro.

In all eyes, fibrosis presented as progressive retrocorneal and retrolenticular membrane formation causing anterior displacement of the intraocular lens and endothelial cell damage with corneal decompensation. One patient experienced a corneal melt and perforation with contracting fibrous tissue anteriorly displacing the IOL into the cornea. Two patients had tractional retinal folds due to posterior extension of the membrane. The initial management in all cases (except cases 3 and 6) included IOL explantation and removal of fibrosis with anterior vitrectomy (one case) or pars plana vitrectomy (eight cases). In seven of nine cases, a type I Boston Kpro was primarily implanted. The patient with the anterior vitrectomy did not initially receive a Kpro, but later experienced progressive corneal decompensation after IOL explantation and subsequently underwent complete pars plana vitrectomy with KPro implantation. In case 6, the Morcher lens was too severely fibrosed to the intraocular structures for safe removal. One patient developed fibrosis in the setting of a previous Kpro and later underwent repeat Kpro implantation because of melting of the carrier cornea tissue (Case 3). In another eye, an Alphacor Kpro, which was initially explanted for a PK, was eventually replaced with a Boston Kpro (Case 8). In 7 cases an aphakic Kpro was used while in 2 cases the IOL was retained and a pseudophakic Kpro was used. All devices (100%) were retained throughout the entire follow-up period of 6 to 48 months (mean 26.1 months).

After Kpro implantation, vision improved in all eyes, ranging from HM – CF preoperatively, to 20/200 – 2/500 postoperatively. One patient (Case 4) was stable after Kpro implantation for 12 months with a vision of 20/200, but after silicone oil removal, developed a suprachoroidal hemorrhage and eventually became NLP. In case 6, where the fibrosed Morcher IOL was retained after Kpro implantation, both tractional retinal detachment and IOL dislocation occurred which required endoscopic repair. Postoperative events after Kpro implantation included retroprosthetic membrane in 5 eyes (case 1, 6-9), suprachoroidal hemorrhage in one eye (case 4) and tractional retinal detachment in one eye (case 6). Figure 1a and 1b show pre and post operative photograph of case 1.

Discussion

Our finding of aniridic fibrosis syndrome in patients with congenital aniridia is consistent with the conclusion by Tsai et al. that increased number of intraocular procedures and hardware implantation is associated with this complication.¹¹ While most patients with congenital aniridia tolerate multiple procedures without complication, a subset appears to develop anterior chamber fibrosis. As found in both of our studies, this syndrome is characterized by the development of progressive anterior chamber fibrosis and the development of a fibrotic membrane that appears to originate from the rudimentary iris. As the fibrous process progresses it can cause anterior displacement of the IOL with

corneal decompensation. Posterior growth of the fibrotic membrane has been shown to cause hypotony when the membrane reaches the ciliary body with retinal traction when the membrane reaches the vitreous base.¹¹ Tsai et al found that removal of the membrane from the ciliary body reversed hypotony.¹¹

An interesting feature of aniridic fibrosis syndrome is that initiation and progression of fibrosis can occur in the absence of clinically detectable inflammation.¹¹ In addition, poor wound closure that is common in fibrous ingrowth was not detected in our cases. While the etiology of aniridic fibrosis syndrome is not completely understood, irritation of immature blood vessels in the rudimentary iris in the setting of surgery and chronic friction of this abnormal tissue with intraocular hardware has been suggested to play a role in its development.¹¹ In fact, intraocular devices can be a stimulator for fibrosis and can act as a scaffold for progression. It is possible that the biocompatibility response is different in these abnormal eyes. In addition, mutation of the *PAX6* gene may contribute to its development as similar intraocular fibrosis has been seen in Peters anomaly after intraocular surgery.¹¹ On histopathology, the fibrotic tissue of aniridic fibrosis syndrome contains dense hypocellular fibrous connective tissue. Previous examination of these membranes has shown no glial, corneal, endothelial, lens epithelial, or lens capsular elements, which suggests that the membrane is not embryologic nor the consequence of regional proliferation of ocular structures.¹¹ As compared to other retrocorneal membranes, such as after multiple surgical procedures or corneal scleral lacerations where the fibrotic membrane is thought to arise from fibroblastic proliferation of the cornea stroma through breaks in the endothelium, the fibrotic membrane of aniridic fibrosis syndrome arises from the iris and moves anteriorly towards the cornea.¹² The most similar clinical entity is a cocoon-like fibrous membrane enveloping the IOL after cataract surgery that has been reported in patients with chronic uveitis.¹³ Yet, as noted by Tsai et al and verified in our study, patients with aniridic fibrosis syndrome do not appear to have clinical or histological signs of significant chronic inflammation.¹¹

There is a report of success with Boston Kpro in aniridic patients. Akpek et al published a series on Boston Kpro implantation in 16 aniridic eyes with successful outcomes in terms of retention rate and visual improvement.¹⁰ We specifically used the Boston Kpro for a subset of aniridic patients with anterior fibrosis syndrome. Another recent report has described the use of the Boston Kpro with pars plana vitrectomy and silicone oil fill to improve vision and maintain globe structure in 13 hypotonus eyes including 5 eyes with aniridic fibrosis syndrome.¹⁴

In our study, surgical intervention consisted of IOL explantation (except in cases 3 and 6) and removal of the fibrotic membrane. Case 6 was one of the early eyes in our experience where Kpro implantation was used for aniridic fibrosis syndrome. The Morcher IOL was thought to be too severely fibrosed to the intraocular structures for safe removal which may have increased the risk for

tractional retinal detachment which occurred later after Kpro implantation. This case helped to highlight the importance of removing any intraocular implants present for subsequent cases. Kpro implantation did manage to improve the patient's visual acuity which at final follow-up remained improved to 20/400 compared to HM pre-operatively. There was one case of recurrence during the follow-up period, after the IOL removal and before Kpro implantation, thought to be due to the use of anterior vitrectomy instead of pars plana vitrectomy with residual posterior chamber fibrosis. This case was managed by pars plana vitrectomy at the time of Kpro surgery with no recurrence afterward. All patients experienced improvement in visual acuity, although the improvement was minimal in one patient after exchanging the Alphacor Kpro with the Boston Kpro, because of ocular comorbidities. One patient that had been stable for 12 months after Kpro experienced a suprachoroidal hemorrhage leading to complete visual loss immediately following silicone oil removal and opening of the tube shunt which had been tied at the time of the oil placement. Tsai et al noted recurrence in two of three patients treated with IOL exchange, with no recurrence in other patients or after explantation in those two cases.¹¹ These findings suggest that the best therapy for aniridic fibrosis syndrome may be implantation of the Boston Kpro as it avoids the use of an IOL, which is correlated with fibrosis in these patients. In addition, our finding of recurrence after performing anterior vitrectomy suggests that complete pars plana vitrectomy may be necessary for preventing recurrences because of more radical removal of fibrotic tissue.

As aniridic fibrosis syndrome can be visually devastating for patients with already limited acuity, early detection and surgical intervention are highly recommended. We have shown that aniridic fibrosis syndrome can be safely and effectively managed through IOL explantation and removal of the fibrotic membrane with subsequent Boston Kpro implantation. Early intervention is important given the progressive nature of the disease and the difficulty in assessing the progression of the membrane clinically. Patients with aniridic fibrosis syndrome should be carefully monitored with serial A-scan measurements or ultrasonic biomicroscopy, as suggested by Tsai et al.¹¹ Finally, we agree with the previous suggestion to reduce intraocular devices, such as IOL or artificial irides, during surgical intervention in patients with aniridic fibrosis syndrome.¹¹ While Kpro hardware does seem more biocompatible, it is more possible that its location away from the iris root and angle is the reason for its success in eyes with aniridic fibrosis syndrome.

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Figure Legend

Figure 1. Anterior Fibrosis Syndrome in case 1. Recurrent fibrosis after IOL explantation and anterior vitrectomy only (A). The same eye after pars plana vitrectomy and Boston Kpro type 1 showing early retroprosthetic membrane formation (B).