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# Approaches to Retinal Detachment Prophylaxis among Patients with Stickler Syndrome

*Ameay V. Naravane and Polly A. Quiram*

## Abstract

Stickler syndrome is the most common cause of pediatric rhegmatogenous retinal detachments. Given the dramatic long term visual impact and difficult surgical management of these detachments, there is increasing interest in determining whether prophylactic treatment can be used to prevent retinal detachments in this population. However, severity of ocular findings in Stickler syndrome can vary by subtype. Three commonly used modalities to provide prophylactic treatment against retinal detachments in patients with Stickler syndrome include scleral buckle, laser retinopexy, and cryotherapy. While laser retinopexy is the most common approach to prophylactic treatment, treatment settings can vary by specialist. In addition, the decision to treat and manage Stickler syndrome is nuanced and requires careful consideration of the individual patient. After reviewing the literature on prophylactic treatment approaches, this chapter will also over guidelines in management of this complex patient population.

**Keywords:** Stickler syndrome, pediatric retinal detachment, prophylactic treatment, laser retinopexy, scleral buckle, cryotherapy

## 1. Introduction

Originally described in 1965, Stickler syndrome is a multiorgan system connective tissue disorder with an estimated incidence between 1:7500–1:9000 births [1, 2].

To date, Stickler syndrome has been reported to be caused by mutations in seven genes including COL2A1, COL11A1, COL11A2, COL9A1, COL9A2, COL9A3, and LOXL3 [3]. Mutations in the first three genes are inherited in an autosomal dominant pattern, while mutations in the latter four genes are inherited in an autosomal recessive pattern. These genes are associated with formation of collagen type II, IX, and XI [4].

Ocular manifestations of Stickler syndrome can be seen in 95% of patients [3]. The hallmark ocular finding of Stickler syndrome is vitreous abnormalities, seen in 40% of patients [4, 5]. Patients also present with high myopia (90%) and congenital cataracts (30%) [4, 5]. 40–80% of Stickler syndrome patients can develop retinal

detachments, which makes it the most common cause of inherited pediatric retinal detachments [4–9].

Given its multisystem manifestations, as ophthalmologists, it is important to be aware of both the ocular and systemic clinical manifestations of this disease. Additional common clinical findings often include craniofacial abnormalities (84%), hearing loss (70%), and arthropathy (90%) [3]. Finally, early arthritis is common among all patients with Stickler syndrome. Other spinal abnormalities have also been reported including scoliosis and kyphosis with resulting chronic back pain affects the majority of adults [3].

Stickler syndrome Type 1 (STL1) is primarily due to autosomal dominant mutations in *COL2A1* and accounts for 80–90% of cases [3, 10]. While the majority of individuals with *COL2A1* mutations exhibit systemic signs, individuals with other variants of the COL2A1 mutation may present with only ocular symptoms. Craniofacial abnormalities are common and are typically due to underdevelopment of the maxilla and result in midface hypoplasia, micrognathia, and Pierre Robin Sequence. Sensorineural hearing loss is the most common type of hearing loss seen in Stickler syndrome, however STL1 typically has a milder presentation of hearing loss. On the other hand, STL1 is associated with the highest rate of RD (60–74%) of all the subtypes [7]. A summary of the prevalence of each type of Stickler syndrome and the associated retinal detachment rate can be found in **Table 1**.

Stickler syndrome Type 2 (STL2) is less common than STL1 but is due to autosomal dominant mutations in *COL11A1*. Craniofacial abnormalities such as midfacial and nasal bridge flattening are typically less pronounced. Approximately 1/3 of patients have variable manifestations of midline clefting (for example bivid uvula, high arched palate, or cleft palate). On the other hand, more severe early onset hearing loss is much more common in type 2 than type 1. 45% of patients with STL2 have been estimated to have hearing loss, 80% of whom had high frequency sensorineural hearing loss [8]. STL2 has a reported incidence of RD of 42–50%, 19% of which are bilateral, making it the subtype with the second highest RD rate [8].

Mutations in COL11A2, which cause Stickler Syndrome Type 3 is the only gene not associated with ocular manifestations [4]. It primarily affects joints and can cause mild to moderate hearing loss [9].

| Gene | Stickler syndrome subtype | Percent of Stickler syndrome attributed to this gene | Retinal detachment rate |
|---|---|---|---|
| COL2A1 | STL1 | 80–90% | 60–74% |
| COL11A1 | STL2 | 10–20% | 42–50% |
| COL11A2 | STL3 | Rare | Non ocular form |
| COL9A1 | STL4 | Rare | Reported, incidence unknown[*] |
| COL9A2 | STL5 | Rare | Reported, incidence unknown[*] |
| COL9A3 | STL6 | Rare | Reported, incidence unknown[*] |

[*]*Retinal detachments have been reported in patients with this mutation. However, these reports have only been from case reports of families with these disorders.*

**Table 1.**
*Incidence of retinal detachment by Stickler syndrome subtype.*

Finally, mutations in *COL9A1, COL9A2, COL9A3* result in the autosomal recessive variants of Stickler syndrome (Stickler syndrome type 4-6). There is more limited data on these rarer forms of Stickler syndrome. Unlike the autosomal dominant forms of Stickler syndrome, cleft palates are commonly not seen in Stickler Syndrome Type 4-6 [4]. Among the recessive types of Stickler syndrome (STL4-6), mild to moderate hearing loss has been reported in STL5, while STL4 and 6 tend to have more severe hearing loss [3].

STL4 has been associated with moderate sensorineural hearing loss most pronounced at higher frequencies, femoral head epiphyseal dysplasia, and spinal abnormalities similar to those seen in STL1-3. Retinal detachments have been reported in the literature in a case series of patients with STL4 but because of how rare STL4 is, incidence is unknown. STL4 has also been associated with exudative retinal detachments exudative retinal detachment [4, 11, 12].

In STL5, hearing loss, midface hypoplasia, and a small chin have been reported in small case series. Retinal detachments have also been reported in patients with this subtype [13].

Finally, STL6 has been associated with moderate to profound progressive sensorineural hearing loss and moderate to high myopia. This rarer type of Stickler syndrome has only been reported in seven total families with the biallelic recessive COL9A3 mutation. Cataracts and retinal detachment have also been reported. In contrast to other subtypes, skeletal involvement appears more variable in STL6 [14].

## 2. Rationale for prophylactic treatment

Unfortunately, surgical repair of RRDs in patients with Stickler syndrome is technically challenging because of the vitreous abnormalities and early presentation of these patients [7]. Stickler syndrome patients are likely to develop giant retinal tears and have a propensity for developing proliferative vitreoretinopathy [15]. Pediatric retinal surgeons are highly aware of the extensive and often multiple surgeries that these patients may require. Anatomic success rate after one surgery can vary from 19 to 78%, while 97% achieve successful reattachment with an average of 2.3 surgeries [15].

Visual outcomes after these extensive surgeries are moderate at best. One case series reported that best corrected visual acuity at last follow up (>1 year) was 20/103 [15]. Further discussion regarding the best surgical approach to managing these complex retinal detachments is out of the scope of this chapter. Given the long-term impact these extensive pediatric retinal detachments can have on Stickler syndrome patients, many pediatric retinal surgeons have explored approaches to prevent these complex retinal detachments from occurring. In particular, the use of prophylactic treatment to prevent or reduce the morbidity of retinal detachments has become increasingly employed.

Although definitive evidence supporting prophylactic treatment is lacking, several systemic review articles have suggested a decreased incidence of RD with prophylactic treatment [7, 16, 17]. However, there have been no prospective randomized control trials performed looking at prophylactic treatment of patients with Stickler syndrome. In addition, retrospective case series have not found a clear benefit from prophylactic laser retinopexy in reducing the rate of RDs in their patient cohort [18].

One challenge in developing a consensus regarding prophylactic treatment is that wide variability in treatment modality, technique, and timing varies from study to study. In addition, many studies often rely on a clinical diagnosis of Stickler syndrome

that has not been verified with genetic testing given lack of access. This makes head-to-head comparison of these different studies challenging from both a treatment and patient selection perspective [19]. The three common approaches for prophylactic treatment include scleral buckle, laser retinopexy, and cryotherapy retinopexy. Some have even reported combined use of these approaches, for example, use of both cryotherapy and scleral buckle [20]. Others, in particular those who report use of laser retinopexy, employ a variety of laser treatment protocols that make it difficult to compare efficacy of one treatment approach to another. Much of the early literature regarding prophylactic treatment stem from robust trials using the Cambridge prophylactic cryotherapy protocol, however, cryotherapy is not widely used, especially the U.S. [11].

Given the wide variation in prophylactic treatment approaches, the purpose of this chapter is to provide an overview of the three primary types of prophylactic treatment (laser retinopexy, cryotherapy, and scleral buckle) and review the literature supporting these approaches.

## 3. Cryotherapy

Much of the robust data regarding prophylactic treatment of patients with Stickler syndrome comes from two studies that first popularized the Cambridge prophylactic cryotherapy treatment protocol. The prophylaxis approach consisted of 360-degree cryotherapy, transconjunctivally in a contiguous fashion to the post-oral retina while the patient was under general anesthesia. The cryotherapy lesions were applied "shoulder to shoulder" to ensure continuity of treatment without gaps.

The first retrospective review was published in 2008 and examined a cohort of 204 patients with type 1 Stickler syndrome (confirmed with genetic testing). The cohort was divided into three groups: group 1 consisted of patients who received no prophylaxis, group 2 consisted of patients with bilateral 360 prophylactic cryotherapy, and group 3 included patients who had unilateral surgical repair for a retinal detachment and subsequently underwent prophylaxis in the fellow eye [21]. The study found 73% of patients without treatment developed a retinal detachment, 48% of which were bilateral. In patients with bilateral prophylactic treatment, only 8% developed retinal detachments. Finally in patients who underwent unilateral prophylaxis, only 10% developed an RD.

The results of this trial demonstrated a clear benefit from prophylactic cryotherapy treatment. The study was followed up 6 years later with a larger retrospective comparative case series looking at 487 patients with type 1 Stickler syndrome. The study examined patients who received bilateral prophylactic treatment compared to those who received no prophylactic treatment. 53.6% of patients in the bilateral control group (i.e., no treatment) developed retinal detachment, 10.3% of which were unilateral and 43.3% of which were bilateral. In patients with bilateral prophylaxis, 8.3% developed a retinal detachment, of which 7.9% were unilateral and 0.4% were bilateral [11].

Despite their retrospective nature, together these two studies laid a robust foundation indicating the benefits of prophylactic treatment for retinal detachment in patients with Type 1 Stickler syndrome. Unfortunately, the use of cryotherapy as prophylaxis is limited worldwide.
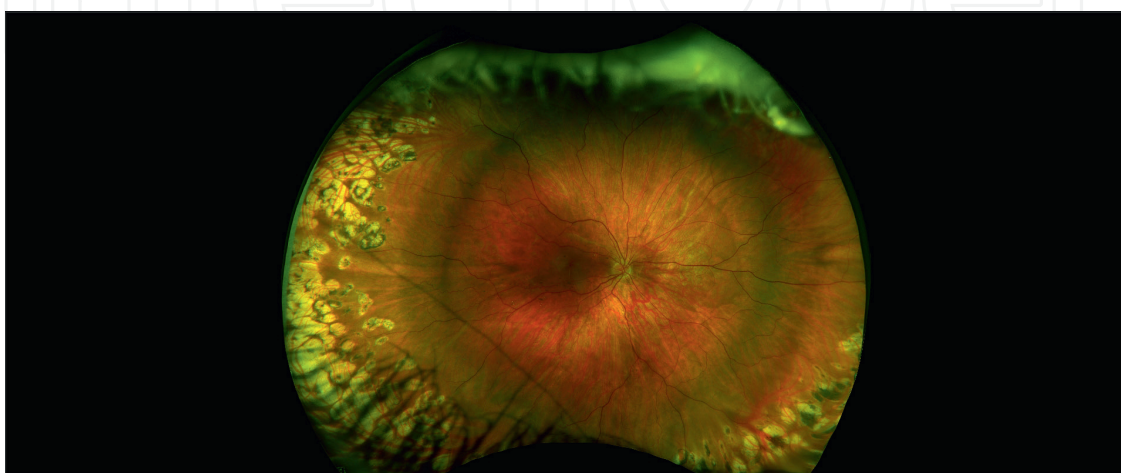
## 4. Laser retinopexy

One of the first retrospective case series that looked at the use of laser retinopexy as prophylaxis for Stickler syndrome was reported in 1996. The series looked at a small family cohort of patients with Stickler syndrome and compared the incidence of retinal detachments in 10 laser treated eyes to 34 non-treated eyes. The study found a 10% detachment rate in the argon laser retinopexy treated cohort [22].

Since then, several studies have looked at use of laser retinopexy. In 2016, a retrospective case series of 70 eyes from 62 patients found a 36.3% rate of retinal detachment among eyes that received prophylactic retinopexy in Saudi Arabia. However, the study lacked a control group and excluded all Stickler syndrome patients who did not develop RDs [18]. In 2018, a case series of 30 eyes from 15 patients with genetically confirmed Type 1 Stickler syndrome demonstrated a 5% detachment rate in patients with laser prophylaxis compared to 50% of patients who did not receive laser treatment [23]. Neither of these case series reported on their laser retinopexy approach, making it difficult to replicate a similar laser protocol.

In 2021, a small case series of 5 eyes from 4 family members with confirmed Type 2 Stickler Syndrome using a two-step laser retinopexy approach, "ora secunda cerclage" (OSC). OSC involves first a laser burn of moderately high intensity placed in a tight grid pattern (one spot width separation) 2 mm onto the pars plana to the ora serrata and 4 mm posteriorly halfway to the vortex vein ampullae. This is followed by an optional step 2 where the laser grid is posteriorly extended to and between the vortex vein ampullae [24]. Although the case series was limited in size, with 8.7 years of follow up, none of the eyes developed a retinal tear or RRD.

In 2022, two additional studies evaluating laser retinopexy were published. The first retrospective case series examined a cohort of 95 eyes from 48 patients and found that the retinal detachment rate was 26.7% among eyes without previous prophylactic laser retinopexy and only 4.6% among eyes with previous prophylactic laser retinopexy [25]. Laser burns of approximately 500 microns applied with a power titrated to a gray-white color in a nearly confluent pattern of 7–10 rows from the ora serrata for 360 degrees was performed in one session (**Figure 1**). The other retrospective case series evaluated patients receiving either extended vitreous base laser (EVBL), non-protocol laser (NPL) or no laser prophylaxis in a group of 230



**Figure 1.**
*Example of prophylactic laser Retinopexy used in patient with Stickler syndrome.*

eyes. There was a 3% retinal detachment rate in the EVBL treatment group compared to a 73% detachment rate in patients who had received no laser retinopexy [26]. EVBL protocol was to treat from the ora serrata to the equator 360 degrees with laser burn spacing between one half to 1 spot size.

Over the past several years there has been a large increase in the number of series reporting positive outcomes using laser retinopexy as prophylaxis for retinal detachments in patients with Stickler syndrome. Laser retinopexy is often preferred to cryotherapy because of its ease of use and more widely spread familiarity. While the evidence supporting laser retinopexy continues to mount, as with the cryotherapy studies, this data is retrospective in nature. In addition, unlike the studies from the cryotherapy group, many of the large studies presented here are based on a clinical diagnosis of Stickler syndrome making it difficult to determine which patients were inherently at a higher risk because of their Stickler syndrome mutation. Additionally, as previously alluded to, each of the studies presented here have a unique approach to the laser retinopexy performed, making even head-to-head comparisons in the laser group alone difficult.

## 5. Scleral buckle

The last commonly used prophylactic approach is use of a scleral buckle. Use of scleral buckle to prevent detachments in patients with stickler syndrome has been reported in the literature as far back as 30 years ago. Retrospective case series in 1994 of 22 patients with "Wagner-Stickler" syndrome looked at rates of detachment in patients with various prophylactic treatment approaches. Eight patients were treated with an encircling scleral buckle but none of these patients developed a retinal detachment [27].

Unlike cryotherapy and laser retinopexy which target retinal adhesions, scleral buckle targets the issue of vitreous traction. However, by addressing the risk of vitreous traction, patients undergoing scleral buckle must also consider the increased risks of a more invasive procedure.

A recent retrospective case series published in 2022 assessed the impact of prophylactic scleral buckle in patients with genetically confirmed type 1 Stickler syndrome whose fellow eyes had a retinal detachment. All scleral buckles were performed by the same surgeon and used a 6 mm wide encircling band [20]. Thirty-nine patients underwent a scleral buckle with cryotherapy while 13 patients underwent a scleral buckle alone. In total, with an average of 15 years of follow up, only five patients developed a retinal detachment, all of whom had only received a scleral buckle alone. 0% of patients receiving both a scleral buckle and cryotherapy had a retinal detachment. Although the results of one retrospective case series must be interpreted with caution, these results suggest that the combination of scleral buckle and cryotherapy may significantly reduce the risk of retinal detachment in patients with Stickler syndrome.

## 6. Management approach

The first step is often determining when to offer prophylactic treatment for RRD prevention in Stickler syndrome patients. Among an International group of pediatric retinal surgeons, the most important factors influencing the decision to

offer prophylactic treatment were a history of retinal detachment in the fellow eye, a family history of retinal detachment, and whether the patient had a high-risk genotype (i.e., COL2A). At the same time, almost half of respondents (41%) offered prophylactic treatment to all patients with Stickler syndrome [28].

Once the decision to provide prophylactic treatment is decided, the type of treatment must then be determined. In this international cohort of pediatric retinal surgeons, 76% reporting using laser retinopexy, 12% used scleral buckle, and 12% used cryotherapy [28].

Similar to what has been reported in the literature, the surveyed group of pediatric retinal surgeons reported using a wide variety in laser technique used. For example, 71% applied laser 360 degrees, 23% applied to visible lattice only, and 6% applied to both visible lattice and 360-degree laser to the vitreous base. The number of rows of laser also varied. 58% applied 3–5 rows of laser, 19% applied 5–7 rows of laser, and 32% applied 7–10 rows of laser. Respondents on average used a spot size of 350 microns (range 200–1500 microns, mode: 200 microns) [28].

Use of scleral buckle was less common in the surveyed cohort. Respondents reported use of scleral buckle ranged from in combination with laser retinopexy in all patients with Stickler syndrome to only those with high-risk genotypes. Other respondents reported use of a scleral buckle only if there was a family history of RD or a history of RD in the fellow eye. Finally, some respondents indicated use of SB for patients with high-risk genotypes, if there was a family history of RD or if there was a history of RD in the fellow eye. Of the respondents using both laser retinopexy and scleral buckle, 50% performed laser retinopexy at the same time as buckle placement while the other 50% performed the two procedures in a staged manner [28].

Cryotherapy was also similarly less common. Similar to the results presented above in Section 4.0, 100% of respondents applied cryotherapy confluently for 360 degrees but 50% reported application of 1 row of cryotherapy while the other half reported two rows. This suggests that while cryotherapy is a viable treatment modality that has robust evidence supporting its efficacy in preventing retinal detachments in patients with Stickler syndrome, its use is limited [28].

Another important step in management is determining what age to offer treatment. Patients with Stickler syndrome often start to develop retinal detachments in young adulthood. One study reported an average age of presentation with retinal detachment at 11 years (3–45 years), however others have reported detachments as early as 18 months [18, 21]. This can pose challenges as patients that young are nonverbal and often may present with detachments much later. In the study group that was surveyed, the recommended age of prophylactic treatment was 4.6 years but ranged from 3 months to 12 years old.

After the decision of when and who to treat have been determined, the follow up interval must also be decided. The majority of pediatric retinal surgeons reevaluated patients between 1 to 6 months after prophylactic treatment was performed. However, the decision as to when patients were to follow up was often heavily dependent on individual patient factors. The same factors that influenced pediatric retinal surgeons' decision to offer prophylactic treatment in the first place (i.e., high risk genotype, family history of RD, and history of RD in fellow eye). In addition, the respondents also mentioned the patients age, monocular status, rural location, activities the child was involved in all also impacted their follow up interval.

If prophylactic treatment was not offered, pediatric retinal surgeons, on average, followed patients every 6 months but this ranged from 3 months to 12 months.

## 7. Conclusions

The overview provided in this chapter offers a starting point into the discussion on prophylactic treatment for retinal detachments in patients with Stickler syndrome. While the evidence for prophylactic treatment of patients with Stickler syndrome is mounting, there is no prospective randomized controlled trial clearly demonstrating this benefit. There are significant challenges to a prospective trial as previously discussed in this chapter including how rare Stickler syndrome is, the varying prevalence of RD depending on subtype, and variations in treatment approach even with the treatment modality. In the interim, this overview can guide ophthalmologists in the treatment of initial management of Stickler syndrome patients.

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The authors declare no conflict of interest.

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None.

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