

Retinal Detachment and Prophylaxis in Type 1 Stickler Syndrome

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Purpose: To report the prevalence of retinal detachment (RD) and results of prophylaxis against detachment from a giant retinal tear in a large cohort of patients with type 1 Stickler syndrome.

Design: Retrospective study.

Participants: Two hundred four type 1 Stickler syndrome patients.

Method: Pedigrees and individuals with type 1 Stickler syndrome were identified from the vitreous research clinic and divided into 3 groups. Group 1 consisted of patients who received no prophylaxis (control group). Group 2 consisted of patients who had bilateral 360° prophylactic cryotherapy (study group). Group 3 consisted of patients referred with unilateral RD for surgical repair and who underwent prophylaxis in the fellow eye (mixed group).

Main Outcome Measures: Retinal status after prophylaxis, with failure of prophylaxis being defined as the development of RD or retinal tears needing further retinopexy.

Results: Of 111 patients who had no prophylactic retinopexy (group 1; mean age, 49 years), 73% (81/111) suffered RD and 48% (53/111) were bilateral. Of 62 patients who had bilateral prophylactic cryotherapy (group 2; mean age, 21 years), 8% (5/62) suffered failure of prophylaxis. There were no cases of bilateral detachments. The mean follow-up period was 11.5 years. In 31 patients who had unilateral prophylactic cryotherapy to the fellow eye (group 3; mean age, 36 years), failure occurred in 10% (3/31) of cases with a mean follow-up of 15.5 years. The prevalence of failure of prophylaxis in treated patients was significantly less than prevalence of RD in untreated patients ($\chi^2_1 = 119.2, P < 0.001$).

Conclusion: Prophylactic cryotherapy substantially reduces the risk of RD in type 1 Stickler syndrome and, in this series, eliminated the risk of bilateral detachments. *Ophthalmology* 2008;115:164–168 © 2008 by the American Academy of Ophthalmology.

Stickler syndrome (hereditary arthro-ophthalmopathy) represents the most common cause of inherited rhegmatogenous retinal detachment (RD). The majority of affected patients have type 1 Stickler syndrome and exhibit a membranous vitreous phenotype associated with mutations in the gene for type II collagen (*COL2A1*) (Fig 1).^{1,2} Other pedigrees exhibit a beaded vitreous phenotype and are associated with mutations in the *COL11A1* gene, which codes for

type XI collagen.^{3,4} Other rarer subgroups of Stickler syndrome remain to be characterized.¹

Patients with type 1 Stickler syndrome are at high risk of visual loss from RD, particularly from a giant retinal tear (GRT).^{5–7} There is a great need to develop and test an effective strategy for prevention of RD in these patients. Previous studies using either laser photocoagulation or cryotherapy have given variable results.^{8–11}

We report the results of a large retrospective analysis on RD prophylaxis in type 1 Stickler syndrome patients. In particular, we were interested in comparing patients who received prophylactic treatment with those who did not to investigate the effectiveness of prophylactic cryotherapy.

Materials and Methods

This retrospective study was approved by the local research and ethics committee. All pedigrees and individuals with type 1 Stickler syndrome, including those with predominantly ocular type 1 Stickler syndrome,^{2,12} who were previously seen or were still under active management were identified from the vitreous research clinic at Addenbrooke's Hospital, a tertiary referral clinic for the diagnosis and management of Stickler syndrome patients. The diagnosis of Stickler syndrome in each patient was made according to previously published clinical diagnostic criteria and confirmed where possible by mutation analysis.¹

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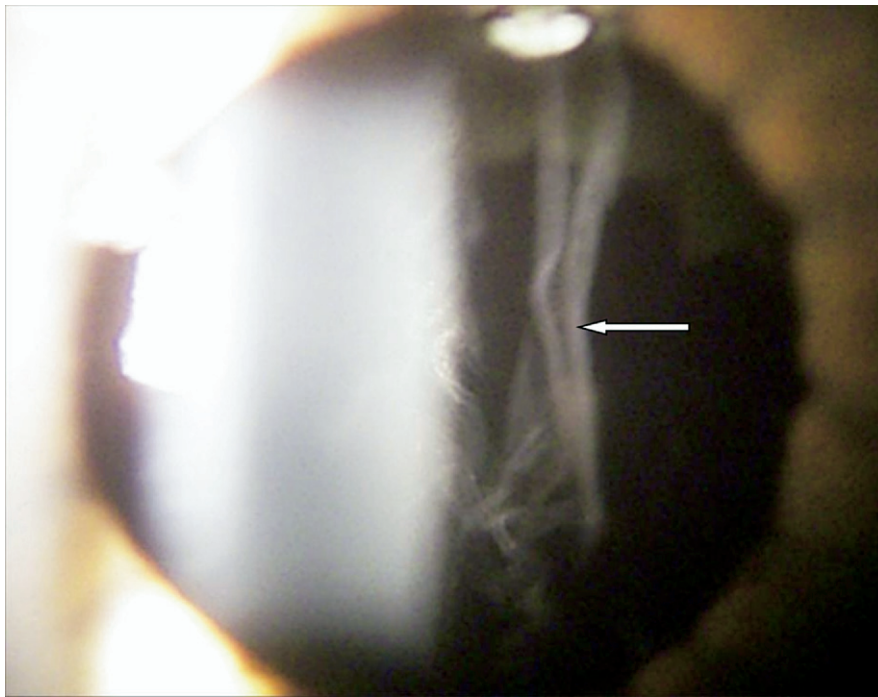


Figure 1. Membranous vitreous anomaly characteristic of type 1 Stickler syndrome.

Information was retrieved by case-note review using a standard pro forma. Data collected for each patient included relevant demographic information and ocular history, including previous RD, whether prophylaxis was given, duration of follow-up (from prophylaxis to latest follow-up), complications of treatment, further retinal procedures after prophylaxis, and retinal status at latest outpatient follow-up. All treated patients had a minimum follow-up period of 1 year.

Prophylaxis consisted of 360° cryotherapy, which was performed with the patient under general anesthesia. Monitored cryotherapy was applied transconjunctivally in a contiguous fashion to the post-oral retina, with the objective of preventing

progression of the posterior flap of the GRT to RD. The lesions were applied touching shoulder to shoulder so as to minimize retreatment of the retina and, in particular, to ensure continuity without gaps (Fig 2a). For the purpose of this study, this technique was classified as standard prophylaxis to distinguish it from other strategies (e.g., treating isolated areas of lattice more posteriorly or using laser retinopexy). Prophylaxis was offered to all Stickler syndrome patients with eyes unaffected by RD.

Mutational analysis was achieved by amplification of large (4–8 kilobase) regions of the 31-kilobase *COL2A1* gene and exon sequencing as previously described.^{12,13} Many of these

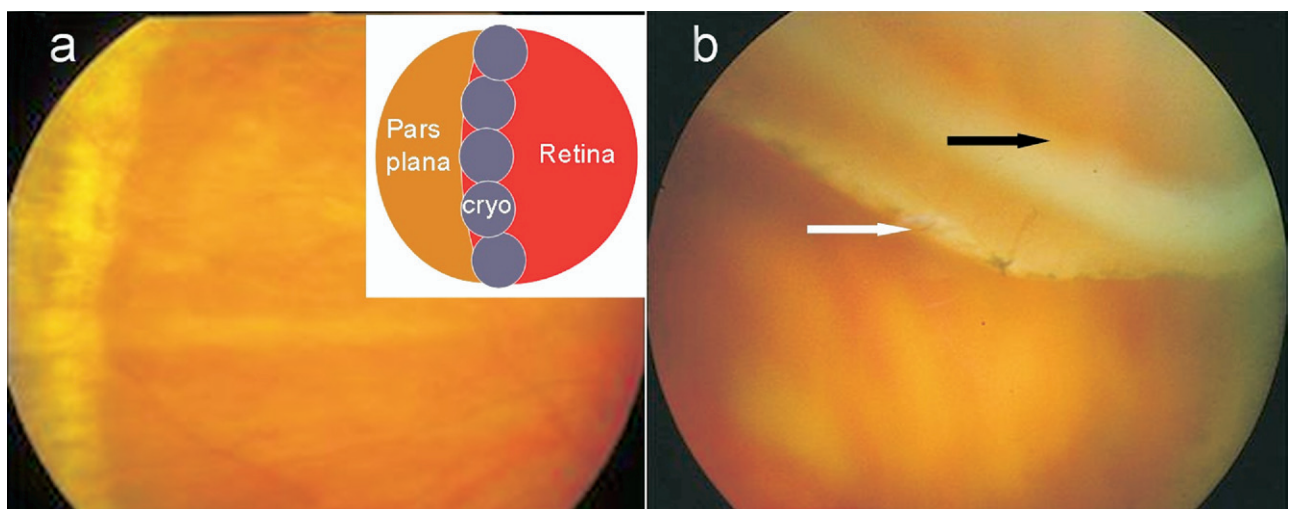


Figure 2. a, Chorioretinal adhesive scars from prophylactic cryotherapy applied just posterior to the ora serrata in a contiguous manner. Inset, Schematic diagram illustrating treatment strategy, with gray circles representing cryotherapy lesions. b, Failed laser prophylaxis (white arrow) that has been placed equatorially and too posteriorly to prevent giant retinal tear progression. Black arrow, edge of GRT.

mutations result in premature termination of translation and nonsense-mediated decay.^{13,14}

The patients identified were divided into 3 groups depending on prophylaxis status:

1. *Control group.* Patients who did not receive standard prophylactic treatment in either eye. They declined treatment offered, already suffered from previous bilateral RD before presenting to us, or were under the care of other eye units. Some received nonstandard prophylaxis. Many did not have continued follow-up in the department. This pool of patients provided an estimate of the prevalence of RD without standard prophylaxis.
2. *Study group.* Patients who had no history of RD and had received bilateral 360° standard prophylactic retinopexy as described above.
3. *Mixed group.* Patients referred to the vitreoretinal service with unilateral RD for repair and who underwent simultaneous standard prophylaxis to the fellow eye.

The main outcome measure of interest was failure of standard prophylaxis in groups 2 and 3. Failure was deemed to have occurred if there was a record in the case note of the treated eye having developed RD or needed top-up retinopexy. The prevalence of failure of treatment in the treated groups was compared with the prevalence of RD in the control patients.

When calculating the prevalence of RDs or failure of treatment, separate calculations were performed using number of patients and eligible eyes as the denominator. In groups 1 and 2, all eyes were eligible to be included in the calculations. Therefore, the number of eligible eyes was double the number of patients. In group 3, however, we were interested only in the prevalence of detachment in the eye that received prophylaxis. The number of eligible eyes was therefore the same as the number of patients.

Data were analyzed using SPSS 13.0 (SPSS Inc., Chicago, IL) and a chi-square test of association with Yates correction for continuity. $P < 0.05$ was considered to be statistically significant. Kaplan–Meier survival analysis using SigmaStat 3.1 (Systat Software Inc., San Jose, CA) was used to compare duration of follow-up and time to failure in groups 2 and 3.

Results

A total of 204 type 1 Stickler patients were identified from the database and divided into the 3 groups as follows (summarized in Table 1):

1. One hundred eleven patients (mean age, 49 years) did not receive standard prophylaxis. There was a history of RD in 81 of 111 (73%) patients, of whom 53 (48%) were bilateral and 28 (25%) were unilateral. Follow-up data were not applicable to this group.
2. Sixty-two patients (mean age, 21 years) received bilateral standard prophylaxis. Mean duration of follow-up after prophylaxis was 11.5 years (range, 1–27). Five patients of the 62 (8%) required further procedures during the follow-up period and were considered to be failures. Four of the failed patients (6.5%) developed unilateral RD requiring surgery, of whom 1 required top-up treatment for posterior holes in the contralateral eye at a later stage. One failed patient (1.5%) required bilateral top-up treatment alone for breaks or holes developing posterior to the cryotherapy barrier. Causes of RDs were as follows: tear posterior to the cryotherapy

Table 1. Demographic Details and Retinal Outcome of Patients Recruited into the Study

	Group 1	Group 2	Group 3
No. of patients (treated eyes)	111	62 (124)	31 (31)
Age (range)	49 yrs (5–92)	21 yrs (3–61)	36 yrs (2–75)
Male:female	55:56	36:26	18:13
Average duration of follow-up (range)	NA	11.5 yrs (1–27)	15.5 yrs (1–33)
No. of patients with RD (%)*	81 (73)	4 (6.5)	3 (10)
Bilateral	53	0	NA
Unilateral	28	4	3
No. of eyes with RD (%)*	134 (60)	4 (3)	3 (10)

NA = not applicable; RD = retinal detachment.

*The differences in prevalence of RD between treated and untreated patients were statistically significant: chi-square test ($\chi^2_{\text{eyes}} = 119.2$, $df = 1$, $P < 0.001$; $\chi^2_{\text{patients}} = 37.0$, $df = 1$, $P < 0.001$).

barrier (1 case), GRT formation with subretinal fluid (SRF) overcoming the barrier (1 case), and tearing of the retina across the cryotherapy barrier (2 cases). The mean time to failure of treatment was 7.7 years (range, 2 months–15 years).

3. Thirty-one patients (mean age, 36 years) received unilateral standard prophylaxis. Mean duration of follow-up after prophylaxis was 15.5 years (range, 1–33). Detachment of retina occurred in the fellow eye in 3 of 31 (10%) patients at latest follow-up. In 2 cases, failure was due to retinal tears posterior to the cryotherapy, and in the third case, the barrier was overcome by proliferative vitreoretinopathy over a period of 5 years. No patient required top-up treatment. Mean time to failure of treatment in this group was 11.6 years (range, 49 months–15 years).

There was no significant difference between the survival curves for groups 2 and 3 (log-rank test: 6.753×10^{-3} , $df = 1$, $P = 0.935$) (Fig 3). The mean age at receiving prophylaxis in groups 2 and 3 was 10 years (range, 2–50).

In summary, of 155 eyes treated with standard prophylaxis 7 (4.5%) developed RD and 3 (2%) required top-up retinopexy during follow-up. In comparison, 134 of 222 (60%) untreated eyes detached. These differences were statistically significant ($\chi^2_{\text{eyes}} = 119.2$, $df = 1$, $P < 0.001$; $\chi^2_{\text{patients}} = 37.0$, $df = 1$, $P < 0.001$).

Complications of treatment were minimal and included transient epiphora, lid swelling, and temporary accommodative paresis. There were no cases of choroidal hemorrhage, macular pucker, or unexplained loss of vision.

Discussion

Retinal detachment represents a major cause of disability in patients with Stickler syndrome, with some series having reported detachment rates of up to 65%.^{5–7} This complication could potentially be reduced if an effective strategy for identification and treatment of patients could be formulated. The issue of prophylaxis in high-risk patients has been addressed by some authors, but most studies to date suffer from small numbers of patients,

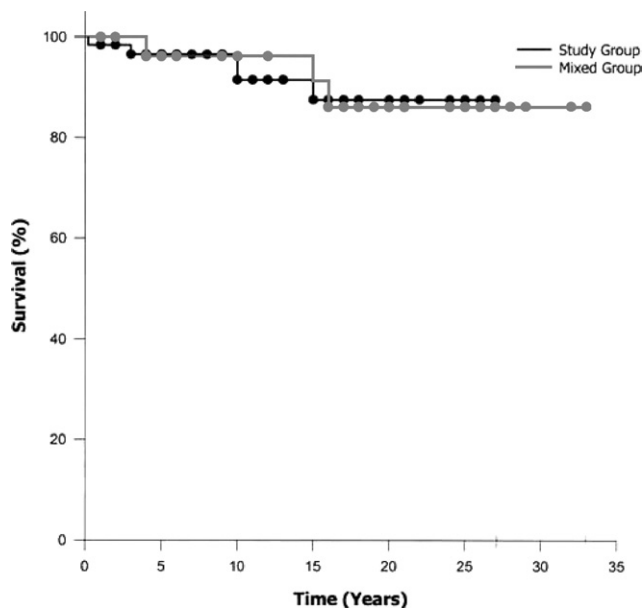


Figure 3. Survival analysis curves for groups 2 and 3. Failure was defined as the occurrence of retinal detachment or the need for top-up retinopathy.

short follow-up, lack of control patients, or heterogeneity of Stickler syndrome subgroups.^{8–11} In this retrospective study, we report on our experience of the effectiveness of prophylaxis in a large homogenous group of patients with type 1 Stickler syndrome.

The rationale and objective of our treatment was to prevent the elevation of the posterior flap of the GRT in the event of its formation during posterior vitreous detachment (PVD) in the predisposed eye. No attempt was made to treat or prevent complications from more posterior pathology. In this study, a GRT was defined not solely by the size of the retinal break, but as a linear tear at the ora serrata caused by an abnormally anterior separation of the posterior hyaloid membrane during PVD. This results in the separation of the pars plana with the formation of a posterior retinal flap that has mobility independent of any associated RD.¹⁵ Treatment placed equatorially or too posteriorly is likely to fail, as the momentum of the detaching retina anterior to the prophylaxis or subsequent induced proliferative retinal shortening may overcome the adhesion (Fig 2b). Similarly, in our experience laser retinopathy did not provide adequate adhesion to protect against RD.

Prophylactic treatment was offered as early as possible and to patients of all age groups once diagnosis was confirmed. The risk of a GRT commences in childhood, the youngest in our experience being 18 months old, and ranges up to the eighth decade. Prevention of RD is especially important in children, as they tend to present late, by which time they may be inoperable.¹⁶ Even with successful reattachment surgery, many suffer from a poor functional visual result. Successful prophylaxis therefore plays a crucial role in the prevention of loss of visual function and disability.

In very young children, diagnosis could be difficult due to poor cooperation with slit-lamp examination of the vitreous. In such cases, treatment was traditionally deferred

until they were old enough for a firm slit-lamp diagnosis to be made, usually at the age of 3 or 4 years, but now it is possible to confirm diagnosis at an earlier age by molecular genetic analysis. On this basis, the youngest patient to receive prophylaxis in this study was 2.

In this study, 73% of control patients (60% of untreated eyes) had suffered detachment of retina, with the majority of them bilateral (48%, vs. 25% unilateral). This result was higher than the prevalence of RD reported in previously reported series.^{5–7} Unfortunately, it was not possible to perform a survival analysis on the control group as there were far too few patients treated by our unit who declined prophylaxis to provide adequate follow-up data for meaningful survival analysis. The vast majority of control patients had RDs that either occurred a very long time ago or were managed by other units. Although ophthalmic history (including previous RD) was explored in all patients, data on the timing of events were either unreliable or missing. Despite this limitation, the control group provides a useful snapshot of the prevalence of RDs in a large group of type 1 Stickler syndrome patients without standard prophylaxis.

In contrast, eyes treated prophylactically with the technique discussed here exhibited a much lower prevalence of RD. Over a mean follow-up period of over 10 years and ranging up to 33 years, failure of treatment (i.e., RD or need for top-up retinopathy) occurred in 6.5% of treated eyes. Time to failure ranged from 2 months to 15 years. The difference in prevalence of RD between control and treated patients was statistically significant. The survival analysis curves of treated groups appeared to plateau after 15 years' follow-up. Extrapolating this trend over longer follow-up, it is likely that the risk of RD will remain much lower in treated eyes than in control group eyes. Furthermore, no patient in group 2 developed bilateral detachment to date. This would suggest that prophylaxis was highly effective in reducing not only the risk of RD but also that of blindness from bilateral detachments.

Comparing the 2 groups of treated patients, there was a higher prevalence of detachment in the fellow eyes of patients who had unilateral detachments (i.e., group 3) than in those of patients with no history of RDs (i.e. group 2), although the difference was not statistically significant. Group 3 patients may represent a subgroup of Stickler patients who were inherently at a higher risk of detachments, possibly influenced by genetic factors. This hypothesis is subject to continued research.

It is unlikely that any strategy for prophylaxis will be universally successful. For instance, detachment secondary to breaks that occur more posteriorly would be neither prevented by this approach nor easily predicted. In this study, 6 of 10 eyes that experienced failure of treatment were due to breaks posterior to cryotherapy (i.e., not GRT related). There is no information in the published literature of the relative frequencies of the different types of breaks causing RDs in Stickler syndrome, and the data from the control group were insufficient to determine the types of causative breaks with accuracy, as many were treated in other units. We may, however, infer from the effectiveness of prophylaxis in the study, and this concurs with our experience, that the majority of RDs are secondary to GRTs.

The other failures (4 eyes) were due to adhesions being overwhelmed by proliferation associated with GRT formation. In 1 eye, the GRT extended over a period of 5 years from 3 clock hours to 9 clock hours before finally breaking through the cryotherapy barrier, whereas in 2 cases, the GRT tore through the retinopexy. In 1 other case, SRF broke through the cryotherapy barrier during GRT formation. It is possible that inadequate adhesion formation in some patients may contribute to failure, although we do not have data to support or refute this.

We have found the treatment to be safe, without long-term side effects. Chemosis and accommodative paresis are temporary. Accommodation in children tended to recover more quickly than in adults (typically 1 month vs. 2–3 months, respectively), based on patient reporting in the postoperative period. Range of accommodation was not assessed formally in this study. There were no cases of macular pucker after cryotherapy. There were also no incidents of unexplained visual loss.

There are unavoidable weaknesses and biases in the current study. First, mean ages of the control and study patient groups were not comparable. Patients in the control group were much older than patients who received prophylaxis, as many of them belonged to the older generations of Stickler pedigrees. Many of them had developed RDs before Stickler syndrome was even described. However, as mentioned above, they provided a useful estimate of the prevalence of RD without standard prophylaxis.

Another potential source of bias included the greater likelihood of Stickler syndrome patients with retinal complication to be included in the control group. Undiagnosed patients with Stickler syndrome may be missed and therefore not included in the study, overestimating the prevalence of retinal complications in the control group. However, the standard practice of the vitreous research clinic was to actively trace and examine as many of the family members from affected pedigrees as possible to detect unknown cases of Stickler syndrome. This practice would have helped minimize the above bias.

Regular follow-up of patients treated with prophylaxis may also help reduce the occurrence of RDs in this group of patients, as new tears detected were treated before they led to RDs. To minimize this bias, eyes that needed further top-up retinopexy were considered as failures in this study even though the retina was not detached. There seemed to be little need for top-up treatment in the treated patients.

Although a mean follow-up of 13 years in groups 2 and 3 (ranging from 1 to 33) was achieved in this study, the risk of RD would appear to be lifelong, so that longer follow-up and ongoing research are needed.

In conclusion, patients with type 1 Stickler syndrome are at high risk of RD, usually affecting both eyes. Prophylaxis with 360° contiguous cryotherapy appears to be safe, with no long-term visual effect, and highly effective in reducing the risk of RDs secondary to GRT within the follow-up period. No treated patient who received bilateral prophylaxis developed bilateral RDs during the study period. Ide-

ally, a randomized controlled study to confirm our findings would be preferable. However, this may raise ethical issues with regard to withholding from Stickler syndrome patients what appears to be highly effective prophylaxis.

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