Supplemental Report

Additional Stickler Prophylaxis Considerations

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Treatment: Cryopexy versus Laser Retinopexy

Despite the desperate need for effective rhegmatogenous retinal detachment (RRD) prevention in Stickler patients who often suffer sight loss at a young age, no reports emulating the Cambridge cryopexy prophylaxis have been forthcoming in 12 years since their first report,[1] or in six years since their second report.[2] While this is likely explained by the rapid movement away from cryopexy to laser-based retinopexy, it may also be due to the rarity of Stickler syndrome (SS), and to an increasing tendency to require level one evidence before accepting any new form of RRD prophylaxis.[3] But during five decades since the advent of laser retinopexy, no clinical trials of retinal detachment prophylaxis have been forthcoming, and such level one evidence is unlikely to ever become available in this rare disease.[2,4]

In the wake of cryopexy abandonment (as RRD repair moved from scleral buckling/cryopexy to vitrectomy/endolaser retinopexy), the few reports mentioning laser prophylaxis for Stickler RRD have not described encircling treatment emulating Cambridge cryopexy treatment crossing the ora serrata junction with the pars plana. This treatment successfully prevented GRT and can be seen in Figure 2 of their 2014 report and in its video supplement.[2] Nor have they described laser treatment sufficiently posteriorly as to reliably prevent the posterior tears that occur in Stickler eyes.[5-9]

Wubben et al recently reported successful laser prophylaxis in 20 SS eyes, with only 5% detaching during six years of follow-up. However, this was mentioned only as an aside in a general report on Stickler syndrome, and no description of the prophylaxis technique was given.[10] A single report of successful slit lamp-based encircling laser prophylaxis in 1996 involved only four eyes, with follow-up lasting as little as one year.[8] Since a mirrored contact lens at slit lamp can reach the ora serrata only with great difficulty,[11,12] this report used the “failed fence” approach, attempting to wall off the entire at-risk peripheral retina rather than treat it.

The Threat: Giant Retinal Tear (GRT) versus Posterior Defects

The 2008 Cambridge report found a 73% prevalence of RRD (48% bilateral) in 111 untreated Stickler patients having an average age of 49 years.[1] The oldest Stickler patient with a new RRD in its 2014 report was 78.5 years of age.[2] Thus, cryopexy limited to the ora serrata in patients averaging 21.5 years of age at treatment likely leaves a substantially higher RRD lifetime risk (usually from new breaks in untreated retina

posteriorly)[13,14] than the 8% failure rate Cambridge documented during a mean 11.5 years follow-up in its first report, or 9.1% during a 5.9 years follow-up in its 2014 report.[1,2]

GRT at the ora, requiring prophylaxis extending onto the pars plana to be maximally effective, occurs in 13% to 50% of Stickler RRD, more commonly in childhood detachments.[5,13-15] One of the three RRDs occurring in the current family was caused by a six clock hour GRT at the ora serrata. Such Stickler eyes can have minimal vitreous adherence posterior to the ora.[2,16] But in other Stickler eyes traction tears occur even posterior to the vortex veins, and multiple tears were seen by Alsharani et al in 50% of RRD eyes.[5]

In a recently published panel discussion of Stickler RRD involving five pediatric retina specialists, all used some form of encircling treatment as prophylaxis in fellow eyes. One surgeon endorsed encircling scleral buckle prophylaxis, while the other four used encircling laser prophylaxis. There was no discussion of posterior Stickler tears or of extending laser treatment posteriorly to prevent them (Retina Times, Fall 2019).

There is no cost in lost visual function when extending retinopexy onto the pars plana anteriorly. But extending retinopexy posteriorly reduces the peripheral visual field, probably accounting for reluctance to apply such treatment, even in Stickler eyes. But we found minimal functional vision deficit even after full Step 2 OSC/SS treatment.[17] When retinopexy is extended posteriorly to the vortex vein ampullae, and between them, it should accurately spare the ampullae and the major choroidal vessels draining into them posteriorly (Figure).

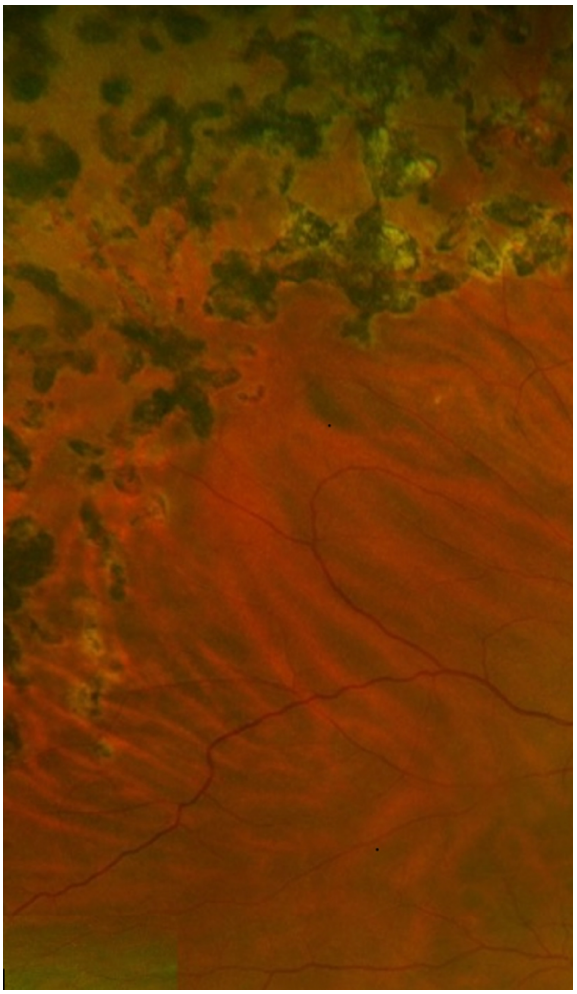

Figure. Retinopexy extending to and around a vortex vein ampulla, at the conclusion of Step 2 OSC/SS prophylaxis.

Treatment Counseling

Desperately seeking a way to prevent RRD, this father and his children sought advice from multiple vitreoretinal specialists who evidently did not themselves perform encircling prophylaxis in SS eyes. According to the father and his three affected children, this option was not presented to them, although two children had been treated with focal laser prophylaxis to visible lattice degeneration. And no one suggested another physician who did perform encircling prophylaxis, or their continued exploration of this possibility, so that they could make their own choice.

Choosing encircling prophylaxis is an easier decision for a Stickler patient who has already lost substantial vision in one eye from retinal detachment, and in whom RRD in the fellow eye is otherwise a probability rather than only a possibility. In fact, the Cambridge natural course study (the most extensive report thus far) showed that bilateralization of detachment occurred in 80% of individuals presenting with RRD in one eye, at a median detachment event separation of only four years.[2] SS patients with extreme myopia are also at especially high risk and might prefer such prophylaxis.[10]

While the application of laser prophylaxis enjoys the inherent safety of being a non-invasive procedure, some risk is involved in any treatment of these unusually fragile eyes, and this must be a part of counseling. Patients/guardians must also be helped to understand that Stickler eyes remain at high risk for months until treatment is completed, and optimal chorioretinal adhesive strength develops.[18] As an example, the daughter in this family suffered RRD within six weeks after discussion of the OSC/SS treatment option before her decision and the procedure could even be arranged. This could easily happen between OSC/SS treatment sessions as well, before substantial long-term risk reduction is achieved.

Patients/guardians must also understand that after laser treatment and healing, the RRD risk is reduced but not eliminated. Years of analysis will be required to define the extent of risk reduction achieved by OSC/SS. Finally, as part of informed consent, only the patient/guardian can accept the modestly increased risk inevitably associated with even a noninvasive treatment, no matter how well performed.

Criticism of encircling laser prophylaxis has included the fact that some eyes are inevitably treated that would not have developed RRD. That is a valid concern and suggests that encirclement should only be performed in eyes determined to be at sufficiently high risk, as in Stickler syndrome, and at the request of well-counseled patients.

RRD in Stickler Children

Because the vitreous cavity is only partially filled with formed vitreous, Stickler patients are susceptible to retinal tears from birth, caused by gel movement that would be impossible in the normal eye during childhood. Recent reports show that the youngest patients suffering RRD were six weeks, three years, four years, and five years of age in various series.[2,5,14,13] In the same series, mean age of all Stickler detachments was 15, 13, 25, and 21 years, respectively.

A substantial majority of SS patients who develop RRD eventually detach in the fellow eye. Unilateral RRD occurs at a mean age of 24.8 years, but patients suffering bilateral RRD suffer first eye detachment much earlier, in adolescence, at a mean age of 15.2 years.[19] And when RRD does occur in childhood, it is typically more difficult to repair. For example, a giant retinal tear appears to be more frequent when detachment

occurs at a young age. Reddy et al reported 50% GRT/RRD in a series with a mean age of 10.6 years,[15] whereas Abeysiri et al reported only 13% GRT in a series with a mean age of 21 years.[13]

A diagnosis of Stickler genotype can now be investigated and confirmed from birth if SS is suspected from family history, upon detection of early-onset myopia, or following RRD at a young age. Prophylaxis for RRD can then begin even in infancy.[16] The earliest Cambridge treatment occurred at just 11 months of age.

After diagnosis in early childhood, we suggest that consideration of prophylaxis against GRT/RRD begin at three years of age with tight grid laser treatment straddling the ora (Step 1). RRD is rare before this age, and the eye reaches adult size by age three.[20] During subsequent examinations, posterior prophylaxis can be gradually increased to completion based on factors such as the family history of RRD at an early age and the parent's ability to monitor (monthly monocular testing for age-appropriate visual acuity, external examinations to confirm straight eyes, and photographic screening for normal retinal reflexes).[21] Alternatively, treatment beyond Step 1 can be deferred until a child reaches an age enabling reasonably informed consent.

These efforts reduce the chance of a Stickler child presenting with chronic, irreparable retinal detachment.[16] However, if a child does so present, we recommend treatment of the fellow eye with both Step 1 and Step 2 OSC/SS.

Persistent Vitreous Traction

Stickler retinal detachments are notorious for both giant retinal tears and for multiple tears posteriorly that are unpredictable as to location.[22] After maturation of OSC/SS laser prophylaxis, effective prophylaxis in some Stickler eyes may ultimately be aided by an especially meticulous vitrectomy (Step 3) to resolve vitreous traction internally. Having been maximally protected from peripheral breaks by laser retinopexy, that is the only additional prophylaxis then possible for the central retina, with a risk in normal eyes now less than 1% in our experience, using 27-gauge, ultra-high-speed vitrectomy probes. We employ special safety precautions when treating symptomatic vitreous opacities (SVO), in order to keep risks as close to zero as possible, and we did so when the Stickler eye mentioned in this article was treated.

In Stickler eyes, symptomatic vitreous opacities might correlate with potential traction from formed cortical vitreous, as Alsharani found veil opacities commonly associated with tears in a large series of SS detachments.[5] Although this is somewhat conjectural, it is worth remembering as we attempt to gain every advantage in the prophylaxis of Stickler RRD. This final Step 3 of SS prophylaxis is reasonably possible in selected eyes of patients who want maximum prophylaxis as a direct result of recent technological improvements in intraoperative viewing and vitreous removal that have substantially reduced the risks and morbidity of treatment.

Conclusion

Frequent GRT, proliferative vitreoretinopathy, and multiple operations using silicone oil are the norm in Stickler RRD.[15] Given the poor prognosis for visual return once detachment occurs, RRD in Stickler eyes is too often a sentence of permanent legal blindness - often in both eyes.[2,5,9,15] Even the minority of Stickler patients who would not have suffered RRD choose encircling prophylaxis based on informed consent and receive the benefit of a lifetime of reduced anxiety regarding potential blindness. Reducing fear of blindness

is itself no small consideration, as is eloquently documented in the book “Touching the Rock,” by author John M. Hull,[23] and in the article by a statement of the father of this family (Video 1).

In Stickler patients, therefore, one can only reasonably argue against encircling prophylaxis for its lack of level-one proven effectiveness or its risk profile, rather than for lack of necessity or for a treatment cost that is dwarfed by a probable lifetime of anxiety or disability in the majority of untreated individuals. Moreover, effectiveness is increased while treatment risk is reduced by attention to the details described herein.

In our opinion, encircling laser prophylaxis failure in Stickler syndrome has been more likely a result of an inadequate technique, rather than an inadequate concept.[5] Said another way, all encircling laser is not the same, yet that is the impression one could easily take from the paucity of encircling laser retinopexy technique discussion in the literature.[5] Good control of laser power density, grid placement, and extent are important to all encircling laser prophylaxis, but are critical to the prevention of RRD in Stickler eyes.

A randomized clinical trial is unlikely ever to be achieved in this rare disease.[4] But the well documented and substantial risk reduction attained by the Cambridge group with cryopexy is impressive, and it can now reasonably be duplicated and likely improved upon via laser retinopexy.

The British Supreme Court issued a Judgment in March 2015 (The Montgomery Judgment) requiring physicians in effect to inform patients not only about treatments the physician believes are reasonable but also those the physician might not provide or agree with but which the patient might reasonably want to investigate. We strongly advise that physicians who examine Stickler patients have an ethical duty to adequately inform each patient of the Cambridge study and the encircling laser prophylaxis option versus the natural course untreated, especially if they do not themselves endorse or offer encircling prophylaxis. It is rightfully the Stickler patient’s choice to make.

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