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The importance of early diagnosis of Stickler syndrome: Finding opportunities for preventing blindness

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Abstract:

Stickler Syndrome (SS) is a significant cause of retinal blindness in children. The immediate cause of blindness is retina detachment from giant retinal tear (GRT). It is frequently diagnosed late and the giant retinal tear (GRT) may be complicated by high-grade proliferative vitreoretinopathy (PVR). The surgery for the combined GRT with PVR has limited structural results and the vision mainly remains impaired. In order to improve the visual outcomes, we propose an organized program oriented toward early diagnosis and surveillance. Adding an effective prophylaxis may maintain normal vision in a high percent of patients. The critical diagnostic moments for this program are prenatal and at birth. The tools include a directed history, general physical exam and advanced ophthalmologic exam looking for the particular features of SS. Some features may need advanced skills transfer, because they are not reliably taught in retina fellowships. Much of this program requires a partnership with obstetricians, pediatricians, neonatologists and geneticists. Finally, we review the evidence regarding prophylaxis and discuss our approach in the absence of guidance from a randomized clinical trial.

Keywords:

Diagnosis, early onset myopia, primary care, prophylaxis, surveillance

Introduction

Stickler Syndrome (SS) remains an unresolved cause of acquired pediatric blindness. In our retina practice, it is a major contributor of unilateral blindness in children. SS was first described by Stickler *et al.*, and results from a mutation in the collagen genes.[1] The common forms are autosomal dominant (AD), and rare forms are autosomal recessive (AR). In the AD genotypes of SS, the main phenotypes are combined systemic and ocular, ocular-predominant, and nonocular.[2,3] SS type 1 is caused by mutations in the COL2A1 gene and is usually characterized by a membranous vitreous and occasionally by a sparse or empty vitreous cavity. SS type 2 is caused by mutations in the COL11A1 gene and is characterized by a beaded vitreous.[3-5] Over the course of three decades, we have discovered a number of barriers to the prevention of blindness in children with SS. We propose that improved outcomes for SS patients depend on the modification of four aspects of management: one, early diagnosis of SS patients; two, early detection of retinal detachment; three, prevention of giant retinal tear; and four, treatment of Stickler giant retinal tear detachment (GRT).

The natural history of SS indicates that blindness results from irreparable retinal detachment. Historically, it was common for giant retinal tear-associated retinal detachment to fail surgical intervention.[6-8] Since the introduction of heavy perfluorocarbon liquids (PFCL) into vitreoretinal surgery, fresh giant retina tear

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outcomes dramatically improved with 90% anatomic success.[9-11] Before the use of PFCL, extremely difficult and hazardous surgery were attempted, included transscleral retinal suturing,[12] retinal scleral incarceration,[6,13] and retina tacks.[14] Good structural outcomes are also common with mild-to-even severe proliferative vitreoretinopathy (PVR).[15] Despite dramatic structural improvement and reattachment; vision gains are limited[9] especially in children.[16] However, cases with both extensive GRT with severe PVR are substantially more challenging. At this level of difficulty, outcomes are often poor[10,15] and variables, such as surgeon experience, assistant experience, equipment, position of the GRT, and unspecified variables, may come into play. These cases are much more technical than the fresh GRT. They also pose a set of surgical challenges and require technical responses outside the scope of this article.

While we can now report successes in GRT and in retina detachment (RD) associated with SS, where there was little hope 35 years ago, we cannot reattach all the cases. Indeed, some remain inoperable, and others while reattached result in no light perception and extreme low vision.[10,15,17,18] Currently, a common pathway to blindness remains a chronic, extensive GRT with severe PVR. A dramatic, but regular scenario, is the presentation of GRT in nonverbal children and teenagers with engorged iris vessels, cataract, or inflamed eye. Ultrasound shows the anterior narrow funnel RD. The prognosis is poor. Indeed, some surgeons may at this point judge the eye inoperable. Based on our experience and the reports in the literature, we conclude, this presentation is too late for reliable positive surgical outcomes. Therefore, the more effective approach to reduce the blindness from SS is the prevention of this highly complex retinal detachment: GRT with PVR. Prevention is a sine qua non.

We consider the last moment for effective intervention to be within few months of the development of detachment. We do not have a timeline for PVR progression; however, it is expected to progress more rapidly with the extensive exposure disinhibition of the retinal pigment epithelium layer that accompanies GRT. Currently, the prompt presentation is reliable only in the second eye after retinal detachment in the first eye. In practice, late detection of unilateral blindness in young children is very common; perhaps even typical. This situation is nicely documented in unilateral cataract,[19] where the finding is externally visible. The intraocular situation of retinal detachment in SS provides few external cues. This lack of signs accompanied by nonverbal or low verbal developmental status delays detection and increases the risk of blindness, despite technical strides in retina surgery.

In our practice, children regularly presented with retinal detachment late (beyond 3 months), and at that time a careful history and physical examination often lead to the diagnosis of SS. In many cases, a parent with mild expression of disease was also discovered. We feel strongly that this pattern contributes to late diagnosis and increased surgical failure. To improve timely detection of GRT, the patients at risk must be identified before the first detachment event and subsequently monitored. In this manner, the retinal detachment may be detected within a few months of the GRT, when the PVR is mild and surgical prognosis improved. In conclusion, to improve visual outcome, avoiding GRT with PVR will reduce blindness. Therefore, we must become advocates for early diagnosis.

A Proposal for Early Diagnosis of Stickler Syndrome

Looking for the critical moments for diagnostic intervention, we note two mandatory physician interactions before the child's detachment. The first is the intake for prenatal care. At that visit, there are three parental diagnostic states as follows: one, the parents know the positive SS status; two, the parents are unaware of their positive SS status, perhaps because they have mild disease; and three, parents with a negative SS status. The typical prenatal questionnaires posted online show no direct attention to this disease.[20] Table 1 lists some proposed strategic questions to add to the prenatal intake.

To identify the first group, the prenatal questionnaire needs to ask about SS directly. This would start a straightforward referral for genetic counseling of affected parents. This is especially important when a parent has a mild phenotype without serious complication and therefore may underestimate the importance of the condition. Type 1 SS is AD and has 50% probability of transmitting the gene to each offspring.[2,3] In the event that the parent reports a diagnosis of SS, the primary care team, including obstetrician and pediatrician, needs to be informed of the risk of airway complications at delivery and subsequent retinal detachment as an infant or child.

The second group of parents may not know their diagnosis, and the diagnosis may be discovered with attention to a more detailed history elicited by the other questions in Table 1. One feature of SS, that is very common and easy for nonphysicians to identify, is early-onset high myopia (EOHM) which is present in both combined and ocular predominant phenotypes.[2,3] This is probably the most strategic (sensitive) first question. Following up with questions about other features (e.g., family history of RD, early-onset cataract, early-onset arthritis, cleft, hearing loss, and Pierre Robin sequence [PRS]) increases the likelihood for the diagnosis of SS. In either case, a patient

Figure 1: Membranous vitreous anomaly in Stickler Disease Type 1 photographed through slit lamp ocular with I-phone: The lens shows smooth reflections and to the right of the posterior lens in the anterior vitreous cavity is a bright reflection off the surface of a vitreous sheet with a light reflex similar to an anterior vitreous face, but showing gentle folds

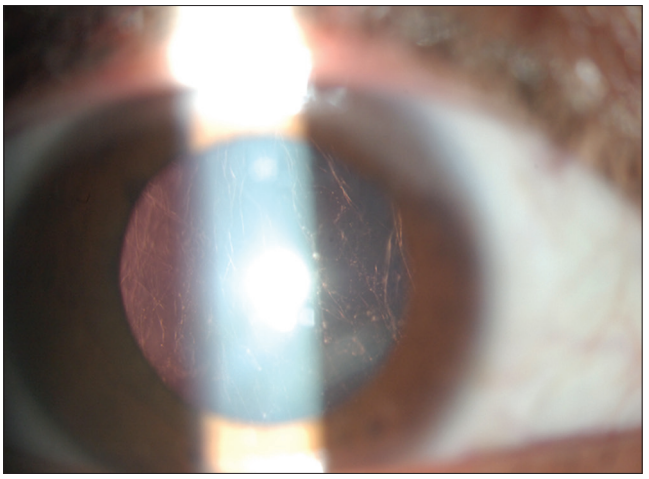

Figure 2: Beaded vitreous anomaly in Stickler disease Type 2 photographed with retro-illumination fibrillar stands with beads are seen. On slit lamp examination, they appear as white light reflex with beads

with EOHM could be referred to an ophthalmologist trained in the details of the eye examination for SS [Table 2]. The most helpful finding is vitreous anomaly with membranous, beaded, optically empty, or fibrillar vitreous [Figures 1 and 2]. Patients with the combination of EOHM and vitreous anomaly or another feature are strong suspects for SS. In addition, very helpful is identification of a normal vitreous. Well-formed vitreous is conceptually incompatible with a collagen defect as seen with SS type 1 and 2. Moreover, we have never observed a well-formed vitreous in SS. However, there are occasional eyes with indeterminate abnormal vitreous. If the vitreous is anomalous and the diagnosis is confirmed the parents must be educated, and the family referred for genetic counseling. The obstetrician must also prepare for a complex airway deliver while awaiting a genetic consultation or molecular testing. The geneticist will also identify subtle nonocular findings of SS [Table 3].

This leaves a small group of undiagnosed parents. The sporadic cases in which parents do not have SS and some very mild inherited cases, for example, mosaics that are clinically unidentifiable in the parents.[21] For this group, the diagnostic strategy requires a postnatal approach that starts with the second mandatory physician interaction: The intake of the newborn by the pediatrician or neonatologist. In this situation, the systemic findings must be detected after birth and any finding can lead to further diagnostic studies. Clearly, all children with cleft palates and PRS will need to be studied for SS, including eye examination and molecular testing.

Ocular predominant is an uncommon phenotype, probably making up <15% of SS patients, and lacks significant systemic features that can lead to diagnosis, the Ophthalmologist must make the diagnosis in these patients.[22,23] The parents may know their status, but sometimes evade the diagnostic suspicion of the ophthalmologists. If they have a history of early-onset high myopia, early cataract, and retinal detachment they will be detected by the prenatal questionnaire. Otherwise,

Table 1: Proposed questions for expectant mothers and fathers

History of SS
History early-onset myopia in a parent and related family
History of RD or blindness in a parent and related family
History of early or childhood cataract
History of cleft palate
History of congenital airway problems
History of joint pain or early arthritis

SS=Stickler syndrome, RD=Retinal detachments

Table 2: Details of eye examination for Stickler syndrome diagnosis

Myopia
Vitreous anomaly: Anterior slit lamp membranous (type 1), beaded (type 2), empty (atypical)
OPTOS vitreous opacity in sheets
OCT dense cortical vitreous
Cataracts (esp cortical and wedge shaped)
Perivascular lattice or pigment disruption

OPTOS=Ultra-wide field retinal imaging (Optos P200Tx, Optos, Scotland, UK), OCT=Optical coherence tomography

Table 3: Characteristic nonocular findings for diagnosis of Stickler syndrome

Incomplete palate: ranges from open cleft, submucous cleft, to bifid uvula
Midfacial hypoplasia in the range of malar hypoplasia, broad or flat nasal bridge, and micrognathia. PRS
Auditory: High-frequency sensorineural hearing loss
Skeletal: Slipped epiphysis, scoliosis, spondylolisthesis, or Scheuermann-like kyphotic deformity, osteoarthritis before age 40. Hyperextensibility

PRS=Pierre Robin sequence

these cases will not be discovered on direct examination at birth. They may join the sporadic ocular predominant cases and pass through both mandatory physician examinations, evading our proposed screening program.

For the ocular predominant phenotype, the Stickler focused diagnostic eye examination is the only clinical method for diagnosis [Table 2]. The examination emphasizes four characteristic ocular findings: early-onset myopia, vitreous anomaly, perivascular pigmentation or lattice [Figure 3], and wedge-shaped cataract. EOHM is observed commonly in SS. However, some pedigrees do not show myopia at any age, and others have a mix of low and high myopia.[23] There is no overall dataset to provide a statistic at this time. In any case, the early onset of myopia less than the age of 5 years, even if <6 diopters may a helpful clinical feature. Myopia even High myopia, is a very common condition and therefore less specific than the 3 other features. These findings make the diagnosis quite likely, but their absence does not rule out the condition. Vitreous anomaly has been documented by slit lamp.[4,5] The vitreous anomaly may also be detected by ultra-wide field retinal imaging (Optos P200Tx, Optos, Scotland, UK) and optical coherence tomography (OCT) especially swept source. However, the predictive value of the new findings has not been systematically determined. The anomaly may change with age and growth of the eye. It may also be undetectable or indeterminate in young children.

The children with sporadic ocular predominant SS probably represent around 5% of cases, and the initial clue is the presence of high or moderate myopia upon the first refraction. This may not occur until school age; however, there is an increase in the use of pediatric vision photoscreening by pediatricians. This would allow detection of early-onset myopia in preverbal children. The next study would be the Stickler eye examination [Table 2]. Under the age of 3 years, examination of the vitreous in children can be challenging. Many children cannot yet sit still and further contributors to risk would be needed before examination under anesthesia (EUA) would seem warranted. EOHM alone raises a suspicion of SS and is an opportunity to review the family history. Is this the first case with EOHM or is this a pedigree with EOHM? If there is a pedigree, then in AD (like type 1) cases a parent is affected. In AR, neither parent is affected by SS; however, similarly affected members may be helpfully studied more easily than the child [Table 2]. However, using a relative's findings as a representative of the child is a best effort and less reliable than a direct examination of the child. Spontaneous RD in parents or their relatives with EOHM increases the need a Stickler-focused EUA. Any break, hole or uncertain abnormality in the periphery is also a strong basis for an EUA.

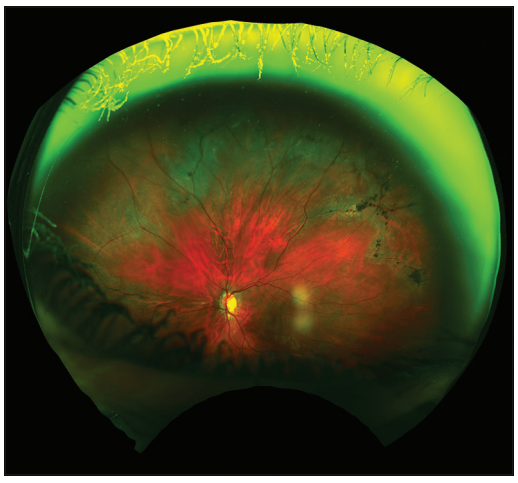

Figure 3: Perivascular lattice: wide-angle funds view of Type 1 Stickler disease patient shows perivascular lattice

Regarding all Stickler type 1 and type 2 patients, we consider the anterior vitreous examination to have great diagnostic power. However, this skill of vitreous examination for anomaly may be underdeveloped in some fellowships without a volume of SS patients. We wonder if this may be also barrier to early diagnosis. We think it could be remedied with the habit of examining every patient with the slit beam in the retrolental anterior vitreous. It is key for distinguishing well-formed, myopic syneresis, age-related syneresis, membranous anomaly, beaded anomaly, and empty vitreous. Appreciation of the frequent fetal residua is also developed through this examination. The timely diagnosis of SS requires knowledge of the syndrome and detection of a characteristic feature that raises the suspicion. Advances in imaging may allow a more reliable diagnosis and reveal new phenotypic features.

Surveillance

Once a patient is diagnosed with SS, we recommend a program of monitoring to detect a retinal detachment within 3 months. This is likely to allow an efficient

Table 4: Surveillance: A program of examinations for children of patients with Stickler syndrome to detect retinal detachments before severe proliferative vitreoretinopathy

Examinations begin at 6 months
Follow-up examinations at 3-4 months interval until reach developmental states that allow clear and reliable communication
Between examinations, the parents are instructed to perform home examinations to detect change in unilateral vision (cover each eye and test for age-appropriate responses to visual stimuli)
Ultrasound may help augment incomplete examinations and probably detect posterior RD in 85%-90% of cases
EUA at risk estimate 15%: Indicated to follow-up on suspicion and when no examination beyond ultrasound is possible
Special examinations after eye trauma events

RD=Retinal detachments, EUA=Examination under anesthesia

repair of GRTs before the development of severe PVR. We consider this guideline a work in progress that will change as more data is collected [Table 4]. Since we have diagnosed a patient at 8 months with a GRT, we suggest a first examination at 6 months. We would follow-up with examinations every 3–4 months. Under age 1 year, the examination would be with a papoose constraint and using Indirect Ophthalmoscope, depressor and speculum. At ages 1–3, there would be no constraint but Indirect Ophthalmoscope at lowest setting and additional study with B-scan ultrasound on each examination. We recommend EUA annually until the child allows a examination of the posterior and equatorial retina. In cases of previous laser prophylaxis, the examination must extend until into the zone of laser-induced chorioretinal atrophy can be seen. EUA is recommended for suspicion of break or retinal detachment or significant trauma. At 3 years or when the child is able to communicate and follow instruction, attempt to train the child with frequent examinations that are rewarded. Continue until around 7 years old or when the child can fully cooperate with the parents and demonstrate clear communication skills. Every month at home we ask the parents to test each eye for normal vision by covering each eye and eliciting responses to age-appropriate visual stimuli.

Prophylaxis and Degrees of Uncertainty

The controversy about prophylaxis is not about whether it is better to prevent a retinal detachment or treat it after it occurs, but rather what is an effective and safe preventative treatment. The discussion of prophylaxis has a few sources of complexity. First, the definitional variability of retina prophylaxis. For example, the prophylaxis for retinal detachment as described by the American Academy of Ophthalmology (AAO) Clinical Education Series, surrounds the retina break and areas of lattice of fellow eyes with three rows of laser,[24] while the Cambridge stickler prophylaxis shows a single row of cryotherapy spots around the retina just behind the ora serrata.[25,26] Our general sense is that prophylaxis is learned during training and therefore the procedure is highly influenced by each surgeon's particular educational lineage. Thus, the term retina prophylaxis may refer to very different treatments both in modality of adhesion and target of adhesion. Second, even with a similar intention of treatment, there is a difference in implementation from physician to physician and case to case; clearly the effect of pupil size and lens opacity will influence the visualization of the target tissue and change the visual feedback. Third, there may be a difference in response among the different phenotypes and subtypes. This complexity may be a source of variability in outcomes which leads to different practice patterns. Certainly, practitioners that have seen poor outcomes after prophylaxis ought not to adopt it as a standard treatment.[27,28]

The Cambridge group has taken effort to standardize and describe their treatment and have presented data that supports its use.[25,26] Their 2014 paper is the best on the topic and has improved on their previous article published in 2008. It has well-defined study sample – type 1 SS, well-defined intervention – single row of cryotherapy applications at ora serrata 360°, well-defined methodology – case-control and follow-up matching. The outcomes show a robust reduction in unfavorable outcomes. The authors recognize that this is neither randomized nor prospective. A randomized controlled trial (RCT) would probably require between 350–500 patients to be powered for a 35% reduction. This is not possible without a very large multicenter study. Although there remains room for bias in the absence of an RCT, it seems to be the best evidence on which to base treatment. Review of case series reporting no benefit after prophylaxis seems significantly less persuasive because of ill-defined selection and treatment.[27,28]

Further regarding the Cambridge protocol for SS, the targeting the area the GRT has a biologic basis. Chorioretinal adhesion in the area that is vulnerable to GRT tears seems more likely to prevent GRT than treatments that induce adhesions in other parts of the retina.[22] We could not find a more detailed description of the cryotherapy treatment for frequent real-life situations, for example, when there is poor visualization because of cataract or poor dilation. We did not find a discussion of the acceptability of a second row of treatment or supplemental treatment for concomitant circumferential lattice. It would be helpful to know if these cases were eliminated from the analysis as part of the "nonstandard treatment exclusion."

The preference of cryotherapy over other forms of chorioretinal adhesion[25,26] (i.e., diathermy or laser) might be an important difference. However, it does not have an obvious compelling biophysical basis.[29-31] We could only provide two rationales for superiority of cryotherapy. One: for treating in cases of compromised media but this is a situational advantage rather than general; and two: avoidance of tissue vaporization that can occur with laser. The precise application of the prophylaxis as seen in the supplemental video requires strong cryotherapy experience and skill that was more common in previous generations. Generally, the laser is an easier skill because it provides more defined and more immediate visual feedback to the surgeon. Laser is the most common and effective method of inducing chorioretinal adhesion throughout vitreoretinal surgery including the surgical repair of GRTs. Therefore, the argument for its categorical inferiority in SS requires evidence beyond historic seniority. Indeed, historical prophylaxis of GRT described by H. Mackenzie Freeman was initially with diathermy and scleral buckle as well as cryotherapy.[32] The

diathermy pattern and use of heat to induce chorioretinal adhesion are certainly more like laser than cryotherapy. In general, the technologic evolution of methods have been continuous and just as the move from diathermy to cryotherapy was made because of ease, it is normative to move from cryotherapy to laser for prophylaxis.

Based on the assumption of equivalence of laser and cryotherapy, in our center, we target the area of GRT from ora posterior for about 10 rows of laser delivered by LIO. The well-defined photocoagulation spot provides immediate feedback about the adequacy of the treatment. Our group is awaiting IRB approval for collection of data for retrospective report. However, no amount of retrospective data can resolve concerns of unintended bias. Prospective data are superior, and a RCT will be most helpful. Our only concern about the Cambridge protocol is the skills for using cryotherapy may not be easy to transfer, confirm or document.

While SS prophylaxis is targeted to the GRT, circumferential lattice may also be present, and its treatment may be helpful. The treatment of circumferential lattice is standard; however, perivascular lattice is an uncertain target. Since its association with retinal breaks and tears was not observed and in some cases, it extends to the posterior retina, we choose to treat when it is anterior to the equator, within or near the GRT prophylaxis.

In conclusion, to reduce blindness from Stickler disease an active program of diagnosis must engage our colleagues in Obstetrics and Pediatrics. After a diagnosis is made, a regime of surveillance is needed to prevent blindness. We perform a prophylaxis that targets the location of GRT because recovery of vision after retinal detachment repair is unreliable. Finally, a multicenter RCT for SS prophylaxis is overdue. It will most likely require an international effort.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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