

**STICKLER SYNDROME
SUPPORT GROUP
(SSSG)
Registered Charity: 1060421**

**STICKLER SYNDROME:
A GUIDE TO THE DISORDER
FOR
MEDICAL AND HEALTHCARE
PROFESSIONALS**

**BY
WENDY HUGHES**

INFO 12 11/2006

Text © Wendy Hughes and the Stickler Syndrome Support Group. All rights reserved. No part of this publication may be reproduced or transmitted, in any form or by any means, without permission.



This publication was printed thanks to the generosity of the 2005/2006 4th year Fashion Marketing students, School of Design, University of Northumbria, who raised funds at a charity auction.

Illustrations: Figs 1-8 and 11 by kind permission of the Department of Ophthalmology, Addenbrooke's Hospital, Cambridge.

Figs 9 and 10 by kind permission of Dorset Centre for Cleft Lip and Palate, Poole .

Various sections of the booklet verified by Mr Martin Snead, Dr Philip Bearcroft, Dr David Baguley and Mr Anthony Markus

TABLE OF CONTENTS

1.	WHAT IS STICKLER SYNDROME?	1
2.	THE HISTORY OF THE CONDITION	3
3.	THE FUTURE	5
4.	WHO IS AFFECTED?	5
5.	DIAGNOSING STICKLER SYNDROME	6
5.1.	OCULAR	6
5.2.	ORO-FACIAL	7
5.3.	AUDIOLOGICAL	7
5.4.	MUSCULOSKELETAL	7
6.	DIAGNOSTIC GUIDELINES FOR PROFESSIONALS	8
7.	EYE INVOLVEMENT	10
7.1.	THE VITREOUS AMOMALY	10
7.2.	RETINAL DETACHMENT	11
7.3.	MYOPIA	13
7.4.	LATTICE DEGENERATION AND GIANT TEARS AND HOLES	13
7.5.	PRE-SENESCENT CATARACT	16
7.6.	GLAUCOMA	17
8.	JOINT INVOLVEMENT IN STICKLER SYNDROME	17
8.1.	THREE MAIN CAUSES OF JOINT PROBLEMS IN STICKLER SYNDROME	20
8.2.	DRUG THERAPY	21
8.3.	NSAID'S	21
8.4.	OTHER TREATMENTS	21
8.5.	SURGICAL INTERVENTION	22
9.	UNDERSTANDING GENETICS	23
9.1.	WHAT WENT WRONG	23
9.2.	GENETIC TESTING FOR STICKLER SYNDROME	26
9.3.	IDENTIFYING DNA CHANGES	27

10.	ORO FACIAL ABNORMALITIES WITHIN STICKLER SYNDROME	28
10.1.	CLEFT PALATE	30
10.2.	SUBMUCOUS CLEFT	30
10.3.	BIFID UVULA	31
10.4.	HIGH ARCHED PALATE	31
10.5.	FEEDING DIFFICULTIES	31
11.	OTHER DIFFICULTIES ASSOCIATED WITH CLEFT PALATE	32
11.1.	HEARING LOSS	32
11.2.	HOW THE EAR WORKS	33
11.3.	CONDUCTIVE HEARING LOSS	33
11.4.	TREATMENT FOR OTITIS MEDIA	34
11.5.	SENSORINEURAL HEARING LOSS	34
11.6.	TREATMENT FOR SENSORINEURAL HEARING LOSS	35
11.7.	HEARING LOSS IN ADULTS AND CHILDREN WITH STICKLER SYNDROME	35
11.8.	HEARING TESTS IN CHILDREN	36
11.9.	HEARING TESTS IN ADULTS	37
12.	SPEECH THERAPY WITHIN STICKLER SYNDROME	37
13.	DENTAL AND ORTHODONTIC CARE	39
14.	PROBLEMS DURING ADOLESCENCE	40
15.	GUIDELINES FOR MANAGEMENT OF THE CONDITION	41
16.	THE STICKLER SYNDROME SUPPORT GROUP	42
16.1.	HOW WE STARTED	42
16.2.	WHY WE ARE NEEDED	43
16.3.	WHAT THE SSSG CAN OFFER THE PROFESSIONAL	44
16.4.	HOW THE SSSG CAN HELP THE PATIENT	45
17.	REFERENCES AND PUBLICATIONS (SELECTED SECTION)	46
18.	HOW YOU CAN REACH US	51

1. WHAT IS STICKLER SYNDROME?

Stickler Syndrome (hereditary Arthro-ophthalmopathy, OMIM (*Mendelian Inheritance in Man*) 108300 and 184840) is an autosomal dominant disorder of collagen (connective tissue), resulting in characteristic abnormalities of the vitreous gel with a variable degree of oro-facial abnormalities, deafness and arthritis. It is usually associated with high myopia, which is congenital and non-progressive. There is a substantial risk of retinal detachment, and is the most common inherited cause of rheumatogenous retinal detachment (detachment due to holes or tears in the retina) in childhood. Although the systemic features are widespread, the sight threatening complications are perhaps the most conspicuous and serious manifestation, particularly the risk of giant retinal tears (GRT) which are often bilateral and, if left untreated, lead to **blindness**.

The non-ocular features show a great variation in expression. Children who present with Stickler Syndrome typically have a flat mid-face with a depressed nasal bridge, short nose, and micrognathia (one or both jaws are abnormally small). These features become less pronounced with age. If present, midline clefting ranges in severity from the extreme of Pierre-Robin Sequence (PRS), through to clefting of the hard and/or soft palate, to the mildest manifestation of bifid uvula.

There is joint hypermobility which declines with age or is lost completely and degenerative arthropathy of variable severity may develop by the 3rd and 4th decade of life. Joint pain, of varying degrees, is a problem for many affected by this disorder throughout life. By midlife some patients require joint replacement surgery for the hips or knees, and mild spondylo-epiphyseal dysplasia is often apparent radiologically. Sensorineural deafness with high tone loss is usually asymptomatic or mild. Stickler

Syndrome is caused by an embryological problem occurring in utero, and life expectancy is normal.

At least 4 genes that control and direct collagen synthesis are known to cause Stickler Syndrome.

- COL2A1 is responsible for Stickler Syndrome in 75% of those affected by the condition who show the characteristic Type 1 vitreous phenotype which has been classified as Type 1 Stickler Syndrome. This causes 'full' Stickler Syndrome including joint, hearing, eye and cleft abnormalities.

Two other genes are known to cause some of the features of Stickler Syndrome.

- COL11A1 manifests as a characteristic Type 2 vitreous phenotype and again causes 'full' Stickler Syndrome including joint, hearing, eye and cleft abnormalities and has been classified as Type 2 Stickler Syndrome. The main difference between Type 1 and Type 2 Stickler Syndrome is in the abnormal formation of the vitreous gel, which is described in more detail in the Eye Involvement section of this booklet under vitreous anomaly.
- COL11A2 causes a 'Stickler-like' non-ocular syndrome, which affects only the joints and hearing. This condition has now been given the name of otospondylo-megaepiphyseal dysplasia or (OSMED) for short.

In a fourth group of individuals the genetic cause is yet to be determined. Research into Stickler Syndrome is still ongoing to try and identify other genes involved and explain why the different clinical features vary both within and between families.

Recently a report has described a recessive form of Stickler Syndrome that is caused by mutations in the gene for yet another collagen gene COL9A1 that makes up part of the type IX collagen molecule. This protein connects the type II/XI collagen fibrils to other components of the extracellular matrix present in cartilage and vitreous. (A New Autosomal Recessive form of Stickler Syndrome is caused by a mutation in the COL9A1 Gene) Van Camp G. et al: *Am J Hum Genet.*: Sept 2006 79: 449-457.)

2. THE HISTORY OF THE CONDITION

Stickler Syndrome is named after Dr Gunnar B Stickler, who, in 1960, examined a twelve-year-old boy at the Mayo Foundation in Minnesota, USA. The boy had bony enlargements of several joints and was extremely short sighted. His mother was totally blind. Dr Stickler discovered that there were other members of the family with similar symptoms, the first family members having been seen by Dr Charles Mayo in 1887. With colleagues he worked to define the condition, the results being published in June 1965 in the *Mayo Clinical Proceedings*. Dr Stickler tentatively named the condition Hereditary Progressive Arthro-ophthalmopathy. The authors of that report renamed the condition Stickler Syndrome, and it is now known world-wide as Stickler Syndrome.

In 1965 when Dr Stickler defined the condition, it was not possible to accurately diagnose and classify the disorder. There was some controversy when Dr Stickler first published his paper as to whether it was a completely new disorder or just a different manifestation of a previously reported disorder such as Wagner or Marshall Syndrome. Subsequently most of these patients were shown to have Stickler Syndrome. A recent paper concluded that the distinction between Wagner Syndrome and

predominantly ocular Stickler Syndrome is now apparent, the two conditions are both clinically and genetically distinct. (Clinical Characterisation and Molecular analysis of Wagner Syndrome: Meredith SP, et al: *Br. J. Ophthalmol.* Oct 2006).

The situation today is that the condition can be diagnosed by a combination of clinical examination and molecular genetic testing with a high degree of confidence, and can be confirmed in the majority of cases with genetic testing. As mentioned it can also be sub-classified into at least four genetic groups—Type 1, Type 2, OSMED and ‘other’.

However, a survey carried out by the Stickler Syndrome Support Group (SSSG) and others in 1999 showed that the average age of diagnosis for adults was thirty-two years, whilst the average age of diagnosis in a child was 4.2 years, confirming the need to raise awareness, especially amongst GP’s and the medical profession in general.

With the amount of knowledge that has been gained by studying patients with Stickler Syndrome over a number of recent years, it is now possible to assess the risk regarding retinal detachments and hearing loss. Advances in micro-surgical techniques now make it possible to repair retinal detachments with a high degree of success. Using keyhole surgery the back of the eye is filled with either a gas bubble or silicone oil to reposition the retina back in place and hold it there with oil or gas, which acts as a splint keeping the retina stable and the break(s) sealed whilst healing matures to full strength. The level of vision restored after such an operation is variable and will not generally be as good as before the detachment occurred.

Patients are now offered prophylactic cryotherapy treatment whereby a broad ribbon of treatment is applied

to the edge of the retina without any gaps. Whether the patient will encounter a retinal detachment or whether this is a successful treatment is a very difficult question to answer. It can only be properly answered over a life-time study not 10-20 years as the risk is life-long. So far there is reasonable evidence to suggest that it does substantially reduce the risk of a retinal detachment to less than 10% for patients who receive prophylactic cryotherapy. Even if patients present with a retinal detachment after having cryotherapy, it will often have limited the progression so that it is easier to deal with and less extensive, and therefore the visual outlook is better. It must be noted that the view of prophylactic cryotherapy is not universally accepted by all vitreoretinal surgeons and one always needs to balance the risks with the possible benefits for the individual patient.

3. THE FUTURE

In the near future it will be possible to offer patients a 'test' for Stickler Syndrome. The work being carried out at Addenbrooke's Hospital in Cambridge is currently funded on a 'Research' basis, but the hospital is hoping to convert the genetic testing that is possible into a service that can be delivered to patients and their families sometime in 2006. More work is now necessary to identify the other genes responsible for variations between individuals and families.

4. WHO IS AFFECTED?

One in 10,000 persons may be affected by Stickler Syndrome. Some medical professionals believe that as many as 3 in 10,000 persons are affected, and according to the Institute of health website it is estimated that Stickler Syndrome now affects 1 in 7,500 to 9,000 new-borns. It is now believed to be the most common connective tissue

disorder in Europe and the Americas. However, further research is needed to confirm this. As an inherited condition, Stickler Syndrome is normally passed from parent to child. There is a 50% chance of children being affected in this way although there are some recorded cases where it has occurred for the first time, a sporadic mutation. Mildly affected relatives may only become apparent on careful clinical evaluation with a slit lamp examination of the vitreous to determine any abnormalities.

All members of the family should be checked so that those family members not affected can be eliminated, and those affected can be assessed, offered prophylactic treatment against retinal detachment if appropriate and offered genetic advice. It is also important that the non-ocular group is identified. However, the vast variation in expressivity and severity complicates counselling because of the uncertainty in severity in affected offspring.

5. DIAGNOSING STICKLER SYNDROME

As mentioned, the expressivity and severity of Stickler Syndrome is variable, even within a family, therefore patients can present with a variety of symptoms. This can make diagnosis extremely difficult. Patients may or may not have a family history of cleft palate, myopia, retinal detachments and degenerative joint disease, and there are some recorded cases of sporadic occurrence. All the symptoms mentioned below have been clinically or radiologically identified in patients with Stickler Syndrome, and will help to aid diagnosis.

5.1. OCULAR

- Early-onset myopia, usually congenital and non-progressive.
- High risk of retinal detachments, which can occur in both eyes.

- Paravascular pigmentation.
- Pre-senescent cataracts, wedge and comma shaped.

5.2. ORO-FACIAL

- Any midline clefting e.g.
 - Pierre Robin sequence
 - Submucous cleft palate
 - Bifid uvula
 - High-arched palate
- Mid-facial hypoplasia
- Micrognathia

5.3. AUDIOLOGICAL

- Sensorineural hearing loss
- Conductive hearing loss
- Otitis media

5.4. MUSCULOSKELETAL

Clinically

- Hypermobility of joints with a Beighton score of 4 or more.
- Premature osteoarthritis
- Arachnodactyly
- Creaking of joints

Radiologically

- Protrusio acetabuli
- Posterior slip of capital epiphysis
- Flattening of femoral heads
- Broadening of the heads of metacarpal and metatarsal - short 4th and 5th metatarsals
- Metaphyseal widening at knees and ankles
- Flattening of epiphyses

6. DIAGNOSTIC GUIDELINES FOR PROFESSIONALS

Until recently there has never been a published diagnostic criteria, although Mr Snead and his team at Cambridge in the UK use the following criteria to diagnose Stickler Syndrome. Anyone attending Mr Snead's clinic is diagnosed with Stickler Syndrome when the following clinical manifestations are present:

<p style="text-align: center;">Congenital vitreous anomaly PLUS any three of the following:</p> <p style="text-align: center;">Congenital myopia</p> <p style="text-align: center;">Detached retina or paravascular pigmented lattice</p> <p style="text-align: center;">Abnormal Beighton joints +/- arthropathy</p> <p style="text-align: center;">Sensorineural hearing loss</p> <p style="text-align: center;">Mid-line cleft</p>

In 2005 Rose et. al. published a paper outlining the diagnostic criteria with a confirmed COL2A1 mutation, Type 1 Stickler Syndrome. (Rose et al: 'Stickler Syndrome: Clinical Characteristics and Diagnostic Criteria': *Am J Med Genet*:138A:199-207: 2005) In this study the authors concluded that for a diagnosis of Stickler Syndrome the patient required a total of five or more points, and at least one major two-point manifestation from the table shown on the next page.

Oro-facial abnormalities (2 points maximum)

- 2 points Cleft palate – open cleft, submucous cleft or bifid uvula (major)
- 1 point Characteristic face (malar hypoplasia, broad or flat nasal bridge, and micro/retrognathia)

Ocular abnormalities (2 points maximum)

- 2 points Characteristic vitreous changes or retinal abnormalities (lattice degeneration, retinal hole, retinal detachment or retinal tear) major)

Auditory abnormalities (2 points maximum)

- 2 points High frequency sensorineural hearing loss (major)
Age <20: threshold >20 dB at 4-8 kHz
Age 20-40: threshold >30dB at 4-8 kHz
Age <40: threshold >40dB at 408 kHz
- 1 point Hypermobility tympanic membranes

Skeletal abnormalities (2 points maximum)

- 1 point Femoral head failure (slipped epiphysis or Legg-Perthes-like disease)
- 1 point Radiographically demonstrated osteoarthritis before age 40
- 1 point Scoliosis, spondylolisthesis or Scheuermann-like kyphotic deformity

Family history/molecular data

- 1 point independently affected 1st degree relative in a pattern consistent with autosomal dominant inheritance or presence of the COL2A1, COL11A1 or COL11A2 mutation associated with Stickler Syndrome.

7. EYE INVOLVEMENT

Vitreoretinal changes including detachment of the retina are the most serious eye problems associated with Stickler Syndrome. Abnormalities of vitreous formation and gel architecture are pathognomonic of Stickler Syndrome. As outlined, there are two distinct phenotypes that can be recognised.

7.1. THE VITREOUS ANOMALY

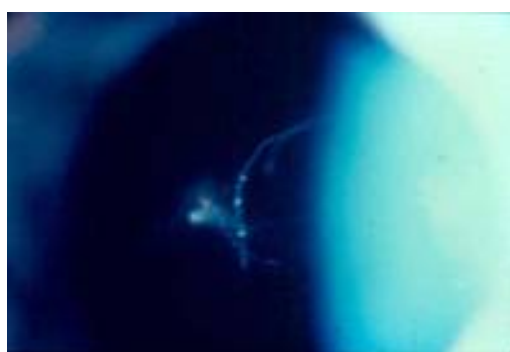
The ophthalmologist using a slit lamp to view the vitreous through the dilated pupil can clearly see the difference between the two types of Stickler Syndrome. This is a valuable tool for ophthalmologists to make a clinical diagnosis of Stickler Syndrome;

Fig 1: Type I Vitreous Anomaly



With Type I Stickler Syndrome there is an abnormal formation of the vitreous gel so that very little is produced and the vestigial remnant occupies the space immediately behind the lens leaving clear fluid in front of the retina.

Fig 2: Type 2 Vitreous Anomaly



In the case of Type 2 the appearance is very different in that the gel fills the back of the eye, but the structure is abnormal and has a different beaded fibrous structure from the general population.

Fig 3: Normal Vitreous



For comparison, the illustration on the left shows a normal vitreous in a patient who does not have Stickler Syndrome.

As mentioned, the majority of patients with Stickler Syndrome have a characteristic congenital anomaly of the vitreous (Type 1) and this correlates with defects in type II collagen. The pathology of Stickler Syndrome in respect of the eye is still unexplored and it is not yet understood why retinal detachment is so prevalent, and the retina so weak.

7.2. RETINAL DETACHMENT

Detachments occur spontaneously and can happen in both eyes. Retinal detachment is more likely to occur in patients with a family history of detachments and often under the age of 30. Retinal detachment in children in the general population is extremely rare, whereas in Stickler Syndrome rheumatogenous detachment is common and should alert the ophthalmologist to suspect Stickler Syndrome

Degeneration of the vitreous means that the fibres come to lie together and strand. These are seen by the patient as floaters and if sudden in onset are often the first symptom that alerts the patient to a possible retinal detachment. Other symptoms of retinal detachment may include seeing flashes of light, black dots, cobweb effects, sparks, or a sensation that a curtain or 'something black' is falling or moving across the eye. These symptoms

frequently occur in the early stages of retinal detachment or with the development of a break or tear in the retina. It is **vital** that the patient recognises these warnings and the help of a vitreoretinal surgeon must be sought immediately.

Failure to do so could result in permanent loss of vision.

When a retina becomes detached, the light sensitive rods and cones become separated from the underlying tissues. The fluid that is normally present inside the eye passes through the retinal tear and lifts the retina from the layer behind, like wallpaper peeling away from a wall.

The most severe detachments can suddenly reduce the vision in the affected eye to almost nothing, and can be very frightening for the person concerned. Early surgery is **vital**.

Due to the formation of retinal tears there is a high risk of retinal detachment, and at the time of Dr Stickler's original report, giant retinal tears were generally considered untreatable and blindness ensued. Modern ophthalmic surgical techniques now allow successful retinal re-attachment and repairs of tears, but the risk of sudden bilateral detachments are a threat in patients with both vitreoretinal phenotypes.

If the retinal detachment operation is successful the patient will be able to see again, but the quality of vision may never be as good as prior to the operation. If gas or silicone oil has been used to press the retina into position, then the retina will not regain full function immediately after the operation, and recovery of sight may take place over many months.

Approximately 90% of retinal surgery is successful, but in Stickler Syndrome retinal detachment is often complex in nature and can occur again because of the development of scarring on the retina.

7.3. MYOPIA

Most, but not all patients with Stickler Syndrome are myopic. Myopia is generally severe i.e. -8 dioptres or higher. Up to -6 is called simple myopia, whilst anything over -6 is termed higher or progressive myopia. Unlike the common onset in the early teens, the myopia associated with Stickler Syndrome is usually congenital, non-progressive, and of a high degree.

7.4. LATTICE DEGENERATION AND GIANT TEARS AND HOLES

Lattice degeneration occurs in about 8 to 11% of the general population in later life, and shows as a linear trail of fibrous vessels within the retina in a 'lattice pattern', but there seems to be a higher incidence of myopia in patients with this problem. These changes include degenerative thinning of the retina, particularly along the blood vessels, and are positioned far back in the retina with characteristic pigmentation along these blood vessels. This is called 'pigmented paravascular lattice degeneration,' and can be seen on the illustration on the next page.

This thinning has several effects: (1) the overlying vitreous will be disturbed, resulting in a pocket of liquid; (2) the vitreous along the edges of the lattice lesion will undergo strong adhesion to the retina, and (3) the retinal thinning will disturb the retinal pigment. After the thinning can become so profound it can lead to a rhematogenous retinal detachment.

Giant tears with large horseshoe shaped holes are also common, and these can lead to sector detachments but, thanks to modern developments, laser and cryotherapy can be used to repair a tear that has already occurred. Both treatments work in an identical way, with laser being used for tears towards the back of the eye, and cryotherapy for tears nearer to the front. The adhesion will take about 10-14 days to mature to full strength. These procedures are usually performed under a local anaesthetic in an outpatients clinic, although some adults as well as children need a general anaesthetic, and are only affective for treatment for retinal holes or weak areas

Since some tears are difficult to close and present long-term complications for the patient, a surgeon may decide to perform another type of operation called a vitrectomy where, under general anaesthetic, the vitreous is removed from the back of the eye by means of a cutter, whilst at the same time the cavity is filled with an injection of a clear substance (air, gas, or silicone oil). Tiny stitches are used to close the wound and do not need to be removed.

Fig 4: Typical Pigmented Paravascular Retinal Detachment

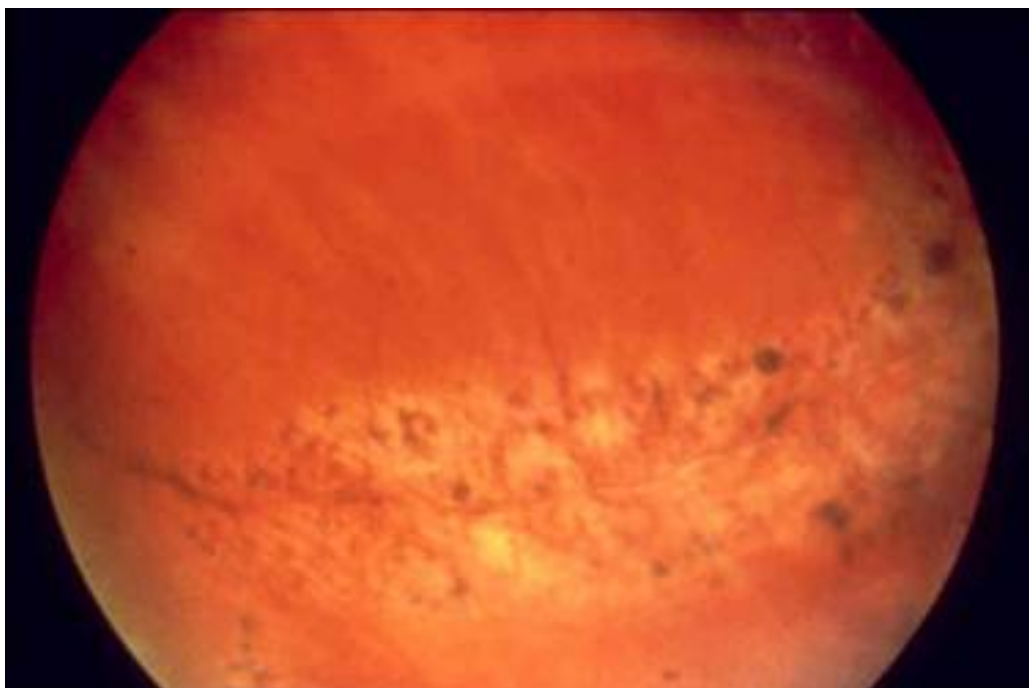
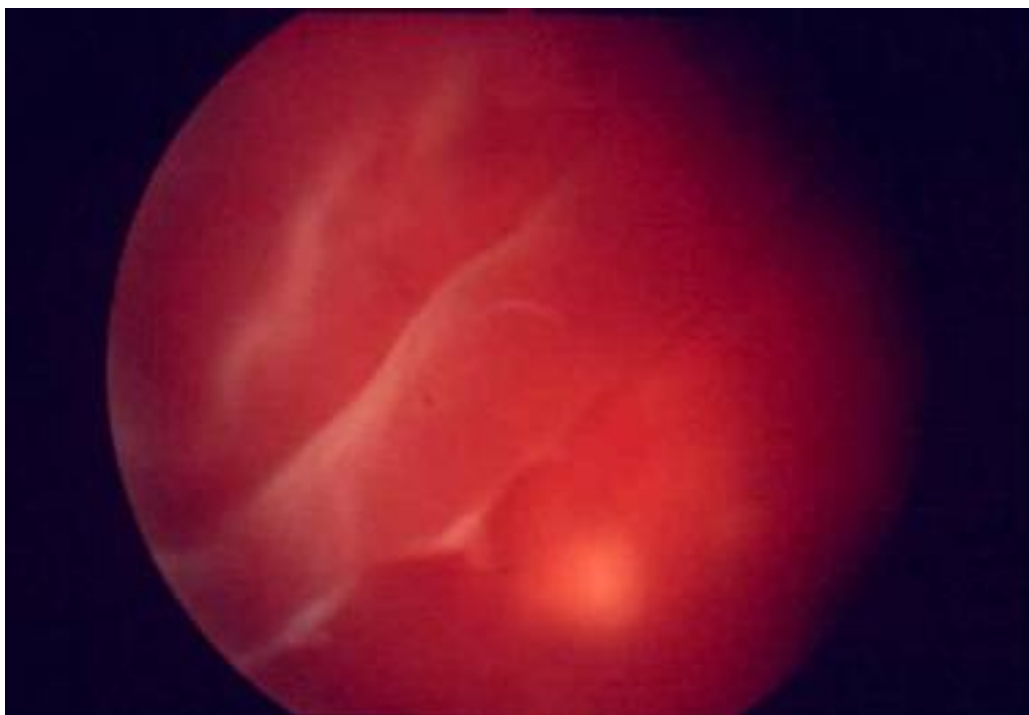
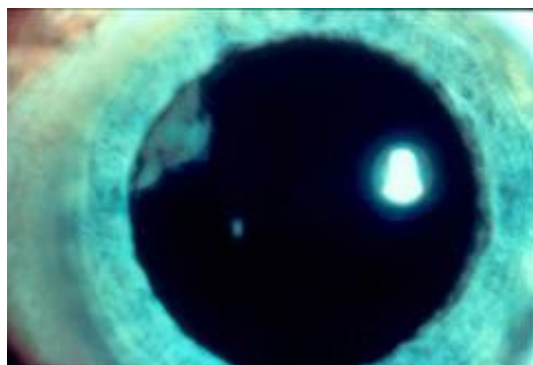


Fig 5: Giant Retinal Tear



7.5. PRE-SENESCENT CATARACT

Fig 6: characteristic cortical cataract.



A cataract is a cloudiness in the lens of the eye. Surgery is the only satisfactory method of dealing with a cataract. Pre-senescent cataracts are common in Stickler Syndrome and may be congenital and non-progressive. Many show an unusual and characteristic curved cortical distribution.

People often describe the effects of a cataract as like 'looking through a mist' or a 'fine chiffon scarf'. The main signs of a cataract developing is a gradual blurring of vision, and as it progresses, the hole of the iris (pupil) looks white or yellow instead of black. As the cataract develops, the patient will notice a slight blurring of vision which can increase in bright light and decreases when dark glasses are worn. Headlights of cars appears like stars and when the sun is low in the sky it will cause dazzle. Usually there is a 'ghosting' like a haze around objects, and occasionally blurring of the entire vision.

The operation to remove a cataract can be performed under either general or local anaesthetic. The operation to remove the cloudy lens takes about half an hour and usually a plastic lens or implant is inserted to correct the focusing of the eye for distance vision. Patients with Stickler Syndrome are normally given a general anaesthetic as the removal of a cataract is slightly more complicated than in the general population, and if the retina is weak can lead to a detachment.

7.6. GLAUCOMA

Developmental abnormalities of the anterior chamber drainage angle predispose patients with Stickler Syndrome to glaucoma.

The eye is kept in the shape of a ball by the pressure of the fluid in the eye. A layer of cells behind the iris produces a watery fluid, called aqueous. This fluid passes through a hole in the centre of the pupil to leave the eye through tiny drainage channels. These are in the area between the cornea and the iris and return the fluid to the blood stream. Normally the fluid produced is balanced by the fluid draining out, but if it cannot escape, too much is produced, the eye pressure will rise, and glaucoma develops.

To reduce the pressure to an acceptable level treatment is usually by eye drops, tablets or both and it is extremely important for the patient to administer these as instructed. If the pressure remains high despite drug therapy a surgeon may decide to recommend an operation to create a new channel for the fluid to drain from the eye and to protect the optic nerve.

8. JOINT INVOLVEMENT IN STICKLER SYNDROME

The degree of joint involvement within Stickler Syndrome is extremely variable. Some people may experience few joint problems, whilst in others the problems are far more significant. Many young patients with Stickler Syndrome have joint hypermobility, and joint mobility should be assessed using the Beighton scoring system to allow comparison with an age, sex and raced-matched population. Typical radiological changes show irregularity of the articular contour with loss of joint space.

Changes similar to osteoarthritis can affect the neck and back and are referred to as cervical and lumbar spondylosis respectively

Prominent joints (e.g. knees and finger joints) are also a feature seen in children with Stickler Syndrome. The symptoms affecting the joints (e.g. pain, stiffness) can be aggravated by excessive overuse. In childhood the features may mimic and are sometimes confused with other forms of juvenile arthritis, or other conditions associated with hypermobility, such as Osteogenesis Imperfecta (OI), Marfan Syndrome, and Ehler-Danlos Syndrome (EDS).

Fig 7: An example of joint Hypermobility. The hands clasped behind the back.



X-ray changes affecting the spine include changes that resemble spondylo-epiphyseal dysplasia which refers to irregularity of the bones of the back (vertebral bodies). These changes can be incidental and cause no symptoms but are helpful in making a diagnosis. Other X-ray changes of dysplasia can be seen to affect the ends of the femur (thigh bone) and other long bones.

Hypermobility of certain joints, can cause the joints to become painful and prone to dislocation. The kneecap, shoulder and even the hip may dislocate, causing pain, although they can usually be returned to the correct position. Children are prone to dislocated joints, and parents and

school teachers should be made aware of this potential problem when a child is playing and exercising.

Hypermobile joints caused by an altered collagen protein in Stickler Syndrome can also lead to hernias or varicose veins. A flat arch to the foot may also be present and this leads to foot ache, particularly when standing for a long period.

In a questionnaire survey of 316 children with Stickler Syndrome (Stickler, Hughes, Houchin: Clinical Features of Hereditary Progressive Arthro-ophthalmopathy (Stickler Syndrome): A Survey: May 2001; *Genetics in Medicine*) 85% of children were reported as hypermobile with enlarged joints. In the adult population of over 40 years 90% reported joint pain with 20% using mobility aids in daily life. In the Stickler Syndrome Support Group UK and European Questionnaire (1999) 83% of adults stated that the knees were the first site of pain, followed by pain in the ankles in children, and pain in the lower back of adults. Some Stickler Syndrome patients will need to be advised to modify their way of life in order to protect the joints and prevent complications, such as the early onset of early osteoarthritis. Like all degenerative conditions, as the cartilage covering the end of the bone wears away, leaving bone rubbing on bone, the joints become stiff, painful and difficult to move.

Fig 8: Right Hip Arthropathy, 28-year old male.



8.1. THREE MAIN CAUSES OF JOINT PROBLEMS IN STICKLER SYNDROME

Rheumatologists now recognise three main causes of joint problems in Stickler Syndrome:

- Joint laxity with arthritis i.e. loose jointedness for which the main treatment is physiotherapy. The patient is given specific exercise to do which are different from those used for patients with osteoarthritis.
- Mechanical problems i.e. knock knees. In this case treatment tends to be appropriate splinting rather than surgery, and removing loose bodies causing the joints to lock. Treatment in this case is usually a washout.
- Fibromyalgia Syndrome, which is not unique to Stickler Syndrome. This can occur independently or linked to another condition. The problem it causes is not due to arthritis as such, but to the soft tissues around the joints. Patients complain of generalised lethargy and fatigue as well as multiple tender points. Fibromyalgia Syndrome is very difficult to treat

since X-rays show nothing. The condition can be responsible for a disturbance in the quality of sleep which in turn affects the pain threshold. Patients may also experience an irritable bowel. Treatment may consist of physiotherapy. Sleeping tablets are not appropriate, but a drug used for treating depression called amitriptyline but prescribed in a much lower dosage (10/12mg) can alter the quality of sleep without sedating the patient. The drug works by altering the pain pathway, although in some patients the effects wear off quickly.

8.2. DRUG THERAPY

Pain-killers, such as paracetamol can help a patient to manage his or her life, but has no anti-inflammatory benefits. The maximum adult intake should not exceed 4 gms per day.

8.3. NSAID'S

Non-steroidal anti-inflammatory drugs can relieve inflammation and are useful for treating mild or chronic conditions.. There are many varieties on the market and the patient may have to try several before finding one suitable for his or her needs. Some patients may not be able to take these drugs if they have other medical conditions.

8.4. OTHER TREATMENTS

Short term relief for symptoms of moderate osteoarthritis of the knee may be obtained from a cortisone injection, particularly if there is some inflammation or fluid in the joint. This is usually recommended under specialist care in conjunction with other treatments and may not be suitable in all cases.

Some Stickler Syndrome patients have found Connective Tissue Manipulation (CTM) beneficial, although this technique is not readily available at all physiotherapy centres. CMT is performed by a physiotherapist trained in this form of treatment. The soft pads of the fingers are used to move one layer of skin on the layer below. The movement creates a short stretch, reflex, thus creating an impulse, which spreads out through the connective tissue. It takes a while for the benefits to take effect and it will not work for everyone. The treatment is intense and tiring for both the patient and the physiotherapist, but it is not painful, just uncomfortable.

A Transcutaneous Electrical Nerve Stimulation (TENS) machine may help some patients to manage pain. They work by the TENS unit sending comfortable impulses through the skin to stimulate the nerve (or nerves) in the treatment area,

A warm bath or heated pillow can relieve pain. Physiotherapists use a number of 'passive' treatments e.g. ultrasound or other treatments using sound waves. Some patients find that hot paraffin was treatment helps finger stiffness.

8.5. SURGICAL INTERVENTION

For those with painful osteoarthritis joint replacement should be considered. Specialist orthopaedic centres should be considered for younger patients, patients with other joint involvement or those needing surgery to correct serious joint deformity.

Arthroscopy: Some individuals (e.g. those with intermittent pain and locking of the knee joint due to loose bodies in the joint) may undergo a keyhole procedure to wash out the knee and remove any loose bodies.

Hip re-surfacing: This a fairly new procedure, so more research is needed into the long-term result as compared with conventional total hip replacement. It is not suitable in all cases, but is now becoming widely accepted as an alternative, especially for younger patients below the age of 60, where revision surgery is likely to be required.

Replacement Surgery: It has now been discovered that patients with Stickler Syndrome require joint replacements surgery at a much younger age than in the general population, so the advent of resurfacing could be the answer for many Stickler Syndrome patients.

9. UNDERSTANDING GENETICS

It is only in recent years that scientists have begun to understand and unravel the wonderful world of genetics. It must be stressed that the only conclusive diagnosis of Stickler Syndrome is through genetic testing.

9.1. WHAT WENT WRONG

Stickler syndrome is caused by a defect in any one of three genes that hold the information for making the collagen present in vitreous and cartilage. There may also be another unknown gene that is defective in Stickler Syndrome.

The genetic information passed on from parents to their children is contained in 22 chromosomes plus the sex chromosomes X and Y. Each person inherits a copy of all 22 chromosomes from each parent and either X and a Y chromosome in males or two X chromosomes in females. These sets of chromosomes contain around 30,000 genes which contain the information required for making the proteins which form the cells, tissue enzymes and other constituents from which our bodies are made. Genes are made of DNA which consists of four molecules

abbreviated to A G C or T and each gene has its own distinct sequence of these 4 letters. Changes to the sequence can alter the information held in the gene and result in inherited disorders, because either the functional properties of the protein which they make, is compromised or the protein may not be made at all.

Stickler Syndrome is a dominantly inherited disorder, which means that only one copy of a gene needs to be defective to result in a genetic disorder. This is in contrast to recessive disorders, where both copies of a gene must be defective. This means an individual with Stickler Syndrome has a 50% chance of passing the defective gene to their children.

The genes that are defective in Stickler Syndrome are called COL2A1, COL11A1 and COL11A2. Only one of these genes needs to be defective to result in Stickler Syndrome. Although Stickler Syndrome is usually inherited, changes to the DNA sequence can occur sporadically during the process of copying DNA as cells grow and divide. This means children with Stickler Syndrome can be born to clinically normal parents as the change may have arisen in the egg or sperm cells from which they developed. In some instances the change to the DNA sequence may be present in only a percentage of cells in one of the parents. These individuals are called "mosaic". This may mean that a 'mosaic' parent appears clinically normal even though they are capable of passing on the defective gene to their children. This may give the appearance of a recessive disorder, but affected children still have a 50% chance of passing the disorder to the next generation.

As mentioned above, in Stickler Syndrome the defective genes are ones which make collagen. There are many different types of collagen in the human body. These have

been numbered with roman numerals in the order in which they were discovered. To date there are 27 different types I-XXVII which have specific functions and can be found in various tissues. The collagens that are defective in Stickler Syndrome are types II and XI. These two collagens make the collagen fibrils that are present in both the vitreous of the eye and cartilage. Whereas one gene (COL2A1) holds all the information for making type II collagen, type XI collagen consists of proteins made from two different genes (COL11A1 and COL11A2). In addition to this the make up of this type XI collagen differs between cartilage and the eye. The type XI collagen in the eye consists only of protein made from the COL11A1 gene, whereas type XI collagen in cartilage consists of protein made from both genes. This means patients with a defect in COL11A2 do not have eye problems in contrast to patients with a defect in COL11A1 that have eye, joint and hearing problems.

Most families have DNA sequence changes unique to themselves and require lengthy and complex gene analysis to be performed on one affected family member to identify their specific DNA alteration. Once this is known it is a relatively simple matter to test other family members. The majority of patients with Stickler Syndrome have defects of COL2A1 and most of these result in only half the normal amount of type II collagen being produced. Changes to type XI collagen affect its function, which is to regulate how the more abundant type II collagen assembles into the fibrils which help to hold the cartilage and vitreous tissues together.

Stickler Syndrome is a clinically variable disorder even within families and it is not possible to predict the severity of the disorder from one generation to another. It is not clear yet what causes this variation but other factors, so of which may also be genetic clearly modify the clinical outcome.

9.2. GENETIC TESTING FOR STICKLER SYNDROME

The three genes known to be involved in Stickler Syndrome are all large and complex. Since most families have changes to the DNA sequence unique to themselves, the identification of the specific change involves a sometimes long, labour intensive and expensive process. Once the change has been found, it is usually a simple matter to test other family members to determine who is and is not affected.

The first problem is deciding which gene to screen for the abnormal sequence. If a family is large it may be possible to perform linkage analysis to exclude two of the three genes. **Linkage analysis** involves identifying the different copies (alleles) of a candidate gene in the parents (there are four, two in each parent) and seeing which if any is co-inherited with the disorder in the children. This is done by using regions of DNA (sometimes called markers) that vary greatly between individuals. These markers are spread throughout the 22 and X and Y chromosomes, so ones that are close to the gene under test are selected. Because parts of chromosomes are shuffled before being passed to the next generation, the closer a marker is to the gene of interest the greater the likelihood is that it will be co-inherited with it, and therefore specifically identify the different gene alleles. In practise three or four different markers in and around the gene are used to identify or “tag” the four different versions of a gene it is possible to inherit from the parents. If all affected children inherit the same allele from an affected parent then this is consistent with the gene being linked to the disorder. If the affected children inherit different alleles then the gene is not linked to the disorder. The larger the family is then the greater the significance that positive linkage becomes. So the more family members that can take part in the analysis the more significant the results can be. It is not possible to

perform linkage analysis in sporadic cases, and in small families statistically significant linkage may not be possible.

It may be possible to identify the abnormal gene by specific **clinical features**. The majority of patients with Stickler Syndrome have defects in the COL2A1 gene, so this might be the first to choose in any case. However differences in the vitreous may also point the geneticist in the right direction. Most patients with defects in COL2A1 have a distinct membrane present in their vitreous gel and this seems to be specific for this gene. Patients with defects in COL11A1 have a vitreous structure, with thickened strands that have a beaded appearance, but it is not yet clear how specific this appearance is with regards to the COL11A1 gene. Patients with defects in COL11A2 have normal eyesight and vitreous gel structure.

9.3. IDENTIFYING DNA CHANGES

There are many methods that can be employed to identify the specific DNA changes that result in Stickler Syndrome. There are advantages and disadvantages to all, but none are capable of detecting all the different types of alterations to the DNA sequence that can cause the disorder. Some methods can be relatively quick and cheap but do not necessarily have an efficient pick up rate. The most reliable are usually more expensive and time consuming. The “gold standard” is to sequence the complete genes. But as they are large, COL2A1 contains over 31,000 letters (or nucleotides) and COL11A1 is even larger at over 250,000 nucleotides, this would prove too expensive. In practice small pieces of the gene called exons, that contain the protein coding regions are amplified (copied many time over to produce enough material to analyse) and then sequenced. This still involves over 5,000 nucleotides each for all three genes.

Patients may be required to give a blood sample for DNA analysis or alternatively a skin biopsy. The skin biopsy is used to analyse the RNA sequence which is the intermediate molecule that is copied from the gene before being translated into collagen protein. DNA can be prepared immediately from blood samples, but skin biopsies have to be grown in culture dishes and this can take up to 3 months before RNA can be prepared from the cells.

Whatever the strategy that is employed to identify this disease causing DNA alterations, it is not a quick easy or indeed cheap process. Doctors and their patients should not expect an answer within weeks. The testing process is not suitable as a tool to confirm a suspicion of Stickler Syndrome. Instead patients should be thoroughly assessed clinically before testing is carried out on those that match the correct criteria.

10. ORO FACIAL ABNORMALITIES WITHIN STICKLER SYNDROME

Fig 9: Baby born with micrognathia



All Stickler Syndrome patients have oro-facial abnormalities to some degree, which will be one or more of the following: A full cleft palate, submucous and/or bifid uvula or high arched palate; glossoptosis, a tendency for the tongue to 'ball up' and fall backwards towards the throat, which could block the airway, and micrognathia (where one or both jaws are unusually small,

resulting in poor contact between the chewing surfaces of the upper and lower teeth). These symptoms are similar to those found in Pierre Robin Sequence (PRS). It has been reported that around 30% of children diagnosed with PRS are later diagnosed as having Stickler Syndrome.

The majority of babies born with PRS have at least two anomalies, a cleft palate and a small lower jaw, and it is interesting to note that over 80% of children presenting with PRS are later diagnosed as having a syndrome of which Stickler Syndrome is a common one. Cleft palate is the fourth most common birth defect, occurring in one in every 700 live births. The cleft is formed by the 4-8th week of pregnancy, before many women are aware they are pregnant, and occurs when the tissues of the face fail to come together leaving a gap, or a cleft. Cleft palates range from a simple notch in the soft palate at the very back of the mouth to a more extensive involvement of both soft and hard palate (the roof of the mouth). It is a repairable defect, although feeding a baby can be difficult at first.

Those Stickler Syndrome children who are diagnosed as having PRS usually have the condition correctly diagnosed at age 6-7 when the print size changes in school and the sight, and possibly the hearing problems, become evident.

The face of a new-born 'Stickler' baby may have characteristic features, which can lead consultants to a correct diagnosis. These include mid-facial hypoplasia, prominent eyes, an epicanthic fold, and a small button nose with little or no nasal bridge. Many of these features, especially the short lower jaw, improve so that the facial abnormalities can look less prominent by the time the child starts school.

10.1. CLEFT PALATE

The timing of a cleft palate repair will vary from surgeon to surgeon. However, most are repaired around the age of 9-12 months. Unfortunately there are no guarantees that this will be the only surgery and many children with a cleft require revision work as they grow. The cleft surgeon will advise, as each case is individual.

Fig 10: Submucous cleft



Fig 11: High Arched Palate



10.2. SUBMUCOUS CLEFT

A submucous cleft is one in which the surface or lining of the soft palate (mucosa) is structurally intact (complete), but the muscles beneath the surface have not joined. Usually the only outward sign of a submucous cleft is a bifid uvula (see below), a bony defect in the hard palate, which looks 'dented' and a bluish or white line in the middle of the soft palate. Early recognition is important as the muscles cannot work properly and so speech and hearing will be abnormal. Unfortunately it is usually not detected until a child develops speech difficulties at around the age of three, but is often detected much later following unsuccessful speech therapy. Children born with a submucous cleft do not always need corrective surgery. If the cleft is not severe enough to create problems, a course of intensive speech therapy is usually enough.

However, in many cases surgery is necessary to restore muscle continuity in order for the child to achieve the kind of function (control) and hearing needed to aid good speech.

10.3. BIFID UVULA

The uvula is the small soft extension of the soft palate that hangs from the roof of the mouth above the root of the tongue. It is made up of muscle, connective tissue, and mucous membrane. Bifid means split into two, therefore a bifid uvula is a split uvula.

10.4. HIGH ARCHED PALATE

A high arched palate occurs when the palatal shelves, which start at each side of the palate, do not come down as far as they should creating an abnormal shaped palate. There is no cleft palate with a high arch palate. However, this abnormal shape can change the position of the tongue and can cause speech problems.

10.5. FEEDING DIFFICULTIES

In order to feed, a baby must be able to form a vacuum inside his/her mouth and position the tongue properly. Babies with clefts may not be able to create this vacuum or position their tongue properly. Some have a smaller lower jaw making swallowing difficult. The cleft team will decide on the best feeding plan to suit mother and baby.

A thin feeding tube may be passed into the baby's stomach though the nose to help those who also have a small jaw. Breast-feeding is rarely possible for those with a cleft palate and a mother should not feel guilty at not being able to feed her baby. Mother's milk can always be expressed. Many babies will need help with feeding by using one of a range of different types of bottles and teats. The cleft team will supply the one best suited to the baby

initially, and the patient will be advised where to buy on-going equipment. In some cases, and in order to help with feeding, an orthodontist may be asked to provide a small dental plate, although there is little evidence to support the theory that they really help with feeding. In some cases a plate may be used to keep the tongue out of the cleft palate prior to repair. Babies with clefts may swallow more air than normal during feeding, especially if the flow of milk is either too slow or too fast. If this happens, it may show by the baby having a blue moustache, being extra sleepy or bringing up some of the feed. If this happens, feeding should be stopped two or three times to burp the baby, or to sit the baby in a more upright position. **Every mother and baby is unique** so it is impossible to give hard and fast rules about feeding. The best method is the one that suits both mother and baby. Try the simple things first, and relax. Allow the baby time with one method before deciding it is not working and before trying alternatives. The secret of success is time and patience and the mother should be encouraged to stay calm.

Babies can lose up to 10% of their birth weight, but will usually regain it in two to three weeks. Babies with a cleft palate may take longer to gain weight.

11. OTHER DIFFICULTIES ASSOCIATED WITH CLEFT PALATE

11.1. HEARING LOSS

There are basically two different types of hearing loss, known as conductive and sensorineural. Individuals with Stickler Syndrome can be affected by either or both. In a child, a persistent hearing loss can affect development of speech and language, social interaction and educational progress. In an adult a persistent hearing loss may affect the patient's ability to communicate, and thus limit social and professional opportunities. There are different

treatments and strategies for managing hearing loss. It is essential that children diagnosed with Stickler Syndrome and/or cleft palate are routinely seen for an audiological assessment to detect any hearing loss as unmanaged loss can impact on speech development and educational performance.

11.2. HOW THE EAR WORKS

Normally sound travels down the ear canal, vibrates the tympanic membrane (eardrum) and the small bones of the air filled middle ear space conduct the sound to the cochlear (the sensorineural part of the hearing system). The cochlear converts the sound waves into electrical nerve impulses which are sent up the hearing nerve to the hearing centre of the brain.

11.3. CONDUCTIVE HEARING LOSS

A conductive hearing loss involves the sound conduction mechanism, that is the eardrum and the bones of hearing (ossicles) within the middle ear. The hearing loss is of a moderate extent. Conductive hearing loss is very common in Stickler Syndrome, and the most common cause of a conductive hearing loss, especially in childhood, is otitis media (sticky fluid causing pressure behind the eardrums). This can be acute or chronic. It is often called glue ear and is due to a malfunction of the Eustachian Tube. The symptoms of otitis media, or other ear infections, can vary from a high fever and lethargy to no physical signs at all. If a child's behaviour changes dramatically – think ears! A well child can develop a full-blown ear infection in just a few hours. A more unusual cause of a conductive hearing loss is a malformation of the ossicle, and Whilst this has been reported in Stickler Syndrome, it does not seem to be common.

11.4. TREATMENT FOR OTITIS MEDIA

If the problem persists it may be decided to perform a minor procedure under general anaesthetic to remove the fluid behind the eardrums and to ventilate the middle ear. A tiny incision (called a myringotomy) will be made in the eardrum, and sometimes to make these incisions more effective, tiny tubes (grommets) are inserted.

If there is still a problem with infections and pressure the procedure may be repeated. If the condition still persists after several sets of grommets, a more permanent set of tubes, called 'T' tubes is inserted through the eardrum. These are held tightly in position behind the eardrum and are usually surgically removed. Aftercare is important and the child's eardrums must be protected from water.

There is some controversy concerning the over-use of tubes in young children, and it is important to remember that all cleft-affected children have an anatomic deformity that reduces the ability of the ear to function normally. This has an effect not only on hearing but also on speech development. In some case of conductive hearing loss a hearing aid may be a safe and effective alternative to surgery.

11.5. SENSORINEURAL HEARING LOSS

Sensorineural hearing loss or 'nerve deafness' is associated with reduced sensitivity of the inner ear to sound. In Stickler Syndrome it is less common than a conductive loss, but may still affect up to 40% of individuals. It is possible to have both a conductive and a sensorineural component to a hearing loss: this is called a 'mixed' hearing loss. It is not known what causes sensorineural hearing loss in Stickler Syndrome, but it is known that the inner ear is rich in collagen and that there are similarities in the cells of the inner ear and the eye.

More research needs to be carried out to establish possible links.

11.6. TREATMENT FOR SENSORINEURAL HEARING LOSS

Sensorineural hearing loss can be managed with hearing aids and therapy if it is causing a problem with education, social or professional activities. It is encouraging to note that the quality of hearing aids has improved considerably over the last few years, particularly with the introduction of digital aids. These more sophisticated modern hearing aids are now available on the NHS

11.7. HEARING LOSS IN ADULTS AND CHILDREN WITH STICKLER SYNDROME

Any baby born with a cleft palate or a family history of Stickler Syndrome should be routinely tested for a hearing loss. If at any time there are any concerns about the child's hearing, speech, language or development a referral to the local Audiology service should be made.

Adults should ask themselves the following list of questions to determine if they need to be assessed for a possible hearing loss:

- Do you feel people are mumbling or not speaking clearly?
- Are you able to hear people, but not understand what they are saying?
- Do you have trouble understanding women, children and soft voices?
- Do you have trouble hearing over the telephone?
- Do you need to turn the television up louder than other people in the household?
- Do you find yourself having to ask people to repeat themselves?

- Do you have trouble following a conversation in a noisy room?
- Do you have ringing in your ears (tinnitus)?

If the answer is yes to any of the above questions then the adult should seek an assessment.

11.8. HEARING TESTS IN CHILDREN

Any child diagnosed as having Stickler Syndrome or Pierre Robin Sequence should be referred to an Audiology Service for a hearing test. Different tests are used depending on the age of the child.

Children up to the age of 8 months of age may be given an oto-acoustic emission test. In a normal functioning ear sound waves, called otoacoustic emissions, are sent out from the ear in response to external sound. By placing a tiny specialised microphone in the child's ear canal an audiologist can measure the signals and investigate the child's hearing. To be able to record these very small sounds requires the child to be fairly quiet. This test can be affected by middle ear effusion and it may be necessary to carry out a second hearing test called an Auditory Brainstem Response test. When the ear receives a sound, a tiny electrical impulse is sent along the auditory nerve to the brain. The auditory brainstem response test records these nerve impulses, and allows the audiologist to establish at what level the child could hear the sound. To carry out this test a series of click sounds is played into the ear through a headphone. The response of the nerve is measured using recording leads placed on the baby's head. As both these tests record very quiet signals, it is helpful if the child is relaxed or better still asleep.

A child between the ages of 8 and 30 months is able to be conditioned to turn to locate an interesting toy when a sound is played. This type of test is called a Visual

Response Audiometry. The child is placed on the parent's lap, and the tester sits in front of the child holding its attention by playing with some toys. A sound is then played from a loudspeaker and the child is taught to look at an interesting puppet or a musical toy which is to the side of the child whenever a sound is played through the speaker. By using this method the audiologist can establish the quietest sound a baby can hear. Other tests may also be used. For example, a test that looks at the functioning of the eardrum, uses a small probe placed in the entrance to the child's ear canal. A microphone then records any sounds reflected back from the eardrum. This test can help to establish the presence of fluid (glue ear) in the middle ear.

11.9. HEARING TESTS IN ADULTS

Adults are usually tested in a sound proof room with an audiometer. The patient is asked to respond when they hear a tone or sounds coming through the headphones. The results are shown on an audiogram, a graph showing the results. Low pitch frequencies (tones) are shown on the left and high frequencies on the right. Soft tones are at the top of the graph and loud sounds at the bottom. The Audiologist will explain the results of these tests, and the types of hearing difficulty will be discussed.

12. SPEECH THERAPY WITHIN STICKLER SYNDROME

In order to speak correctly there must be a good seal between the mouth and the nasal passage. The movement of the soft palate at the back of the mouth, and the movement of the walls of the throat (pharynx) make this seal tight. In individuals with Stickler Syndrome, this seal may be poor if they have a cleft palate or a submucous cleft palate. If this seal is poor then a child will have difficulty in making the proper sounds of consonants such as p, b, t, d, s, and ch. There may also be a nasal

sound to the voice due to air escaping down the nose. A speech and language therapist, who will help the child to speak as well as possible, should routinely check children who experience these problems. When the child is about 9 months old a formal arrangement will be made for the child's speech and language development to be assessed by the speech therapist. Parents should be made aware that until a child's palate is completely closed there are certain sounds that the child will be unable to achieve. If there is a nasal sound in the child's voice, the therapist may use special computer equipment to monitor the air passages as the child speaks. Sometimes a tape recorder and/or a video is used. One of the ways of examining the soft palate and the side walls of the throat is to use a moving x-ray called a video-fluoroscopy. Another method used is called a naso-pharyngoscopy. This involves lightly anaesthetising, with a spray, one side of the nose and then a thin fibre-optic telescope is passed into position to record the palate and side walls of the pharynx (throat) as they move during speech. Nasendoscopy can't usually be done in children under the age of six or seven as it requires considerable cooperation. Following examination, the therapist will design a special programme of activities and sound exercises appropriate to the age and development of the child. The child will be seen again at least annually until five or six years of age. Speech and language will be carefully monitored through to the age of fifteen. These regular assessments will be planned to coincide with primary and secondary surgery, speech development and any later involvement with orthodontic or surgical intervention. If there is a problem that will not improve with speech therapy alone, it may be necessary to improve the seal at the back of the throat with an operation. The surgeon will liaise closely with the speech therapist to ensure that he/she has all the information needed. Once the surgeon understands the particular problem, he or she may then choose to do an operation.

If the nose is not shut off when we speak, air leaks into the nasal cavity and speech becomes nasal in tone as the air that should be used to make sounds in the mouth escapes through the nose. Sometimes this may be due to the soft palate not moving at all, or not enough, so it can't make closure against the back of the throat.. In this situation, taking the palate apart and starting again, re-palatoplasty, or re-do of palate repair, is the best option. If successful, the palate can then function normally and close off the mouth from the nose. However, there are some instances where, despite normal palatal movement, speech is 'nasal'. In these cases, pharyngoplasty is performed. This operation changes the shape of the throat to prevent too much air escaping down the nose, thus helping speech. This operation can also pave the way for therapy to improve speech sounds. A small proportion of children who have their cleft palate repaired in infancy may need a pharyngoplasty to help speech.

13. DENTAL AND ORTHODONTIC CARE

Children who have cleft problems associated with Stickler Syndrome may have malocclusion - poor contact between the chewing surfaces of the upper and lower teeth. Orthodontic appliances or 'braces' are used to apply gentle pressure to the teeth and jaws with the aim of improving the bite or the alignment of the teeth. This treatment is usually carried out in two stages - around the age of eleven or twelve, soon after the permanent incisors (the cutting teeth) and other second teeth have come through, and sometimes again around the age of sixteen or seventeen, when the majority of the permanent teeth have come through. Early orthodontic treatment is aimed at expanding the dental arches if they have collapsed inwards, which sometimes happens after palatal surgery and the formation of scar tissue. Any misplaced teeth can

also treated at this stage and if there is any overcrowding, teeth can be removed to allow the other teeth to erupt into a better position.

Treatment is either with removable appliances or fixed (railway track) appliances depending on the complexity of treatment required. Later orthodontic treatment may be aimed at further improving the dental arches, their relationship to each and the individual position of teeth. Fixed appliances (braces) are invariably used to improve both the alignment and the bite of the teeth with the aim of creating a good dentition - the arrangement of teeth in the mouth. This is important for health, it enables the teeth to function well, and importantly for the adolescent, it is pleasing to the eye. The treatment is generally spread over two years, with monthly or six weekly visits for routine adjustments. This is followed by a retention phase to minimise the possibility of a relapse.

However, when the middle part of the face has failed to grow forwards, as a result of the cleft, surgery (an osteotomy) to advance the bone and the teeth within it, is required. Orthodontic treatment may be a part of this programme, which usually commences as growth is nearly finished, and is designed to ensure that the teeth meet correctly after the surgery has been completed.

14. PROBLEMS DURING ADOLESCENCE

Adolescence is a difficult time for children, but children who have a cleft abnormality may feel self-conscious about their appearance and speech. They may experience feelings of inferiority because they feel different to their peers, and may look and sound different. Time should be spent with the teenager talking through any concerns and worries and they may need to seek professional advice through counselling. Low self-esteem can be a particular problem. Unfortunately, society often

has lower expectations both academically and socially of someone who looks and sounds different. The teenager may also have a lower expectation of him or herself if allowed to believe that their peers and teachers have low expectations of them. Teasing and bullying can be a huge problem for someone who looks different and because of sight and hearing problems the 'Stickler' teenager may find it difficult to make friends and this can lead to withdrawal. On the other hand, in order to assert him or herself the teenager may also become aggressive and disruptive. The adolescent may be regularly absent from school because of medical appointments and surgery and this naturally disrupts his or her social life and creates pressures at school as they can quickly find themselves in a catch-up situation with lessons and homework. Communications can also be a problem. A teacher or peer may misunderstand a child with a cleft problem and this can lead to frustration and bouts of bad behaviour.

15. GUIDELINES FOR MANAGEMENT OF THE CONDITION

Early and correct diagnosis of the condition can significantly help the management of the condition and the outlook for patients. Once Stickler Syndrome is diagnosed, a coordinated multi-disciplinary approach is desirable. This should include:

- A Ophthalmic assessment. Due to the high risk of retinal detachment, all patients also require long-term follow up and are advised to seek ophthalmic help from a vitreoretinal specialist if they see new floaters or shadows in their vision.
- A maxillo-facial assessment where there is evidence of midline clefting.

- Hearing tests and management of combined conductive and sensorineural deafness.
- Joint hypermobility assessment objectively using the Beighton scoring system to allow comparison with age, sex and race-matched population.
- Rheumatological assessment and follow-up is advised for older patients who may benefit from physiotherapy for arthropathy.
- Educational assessment for children. Although intelligence is normal, patients for school age may be considerably educationally challenged because of combined visual and auditory impairment.

16. THE STICKLER SYNDROME SUPPORT GROUP

16.1. HOW WE STARTED

The Stickler Syndrome Support Group (SSSG) in the UK was founded by Wendy Hughes in 1989. In October 1994 the Group held its first conference in Birmingham. More than 100 people attended from all corners of the UK, as well as from the Netherlands, and Eire. Dr Gunnar Stickler, who identified the condition in 1965, came over from America for the conference and accepted the Group's invitation to become their Life President.

In 1995 Wendy Hughes published her book **Stickler The Elusive Syndrome**, which was warmly welcomed by both medical professionals and families. It is still the only book published on the condition, and a new revised edition is now available.

In January 1997 the SSSG was granted charitable status and successfully applied for a 3-year grant from the National Lottery Charities Board. Three months later a Development Officer was appointed to raise awareness of Stickler syndrome and to develop the group beyond its present voluntary capabilities, and Wendy Hughes was officially recognised as SSSG Founder and Honorary President.

The Group continues to fluctuate as members who learn to cope drop out and newly diagnosed families thirsty for information and support join. More than half the enquiries come from the medical profession, and health care professionals who are supporting a family with the condition.

16.2. WHY WE ARE NEEDED

Stickler Syndrome is a common but little recognised genetic disorder as mentioned earlier. Symptoms are variable and can present in different ways even within the same family. When a symptom appears, it is usually treated in isolation by a health professional from one particular discipline (e.g. ophthalmologist, cleft team member, rheumatologist, or an audiologist). Unless all these professionals are aware of the wide range of symptoms which are characteristic of Stickler Syndrome a diagnosis may not be made where there is no clear family history of the condition.

By raising awareness of Stickler Syndrome amongst medical and health-care professionals, and providing accurate and factual information through our literature and our website, we provide a vital service.

16.3. WHAT THE SSSG CAN OFFER THE PROFESSIONAL

- Invite them to join our mailing list so that they can receive all SSSG publications
- Offer a booklet entitled Stickler Syndrome: A guide to the Disorder for Medical and Healthcare Professionals
- Offer a booklet entitled 'Stickler Syndrome A Child in Your Care? What teachers and Youth Leaders Need to Know'.
- Offer booklets on various aspects of the condition for their patients or clients.
- Findings of the UK and European SSSG Questionnaire Survey 1999
- A book and a film on the condition (see pages 40-41)

The SSSG is a voluntary organisation relying solely on donations to provide information and support for people affected by Stickler Syndrome and professionals who have contact with sufferers. The office is manned during the day by a volunteer and a 24-hour answerphone service is provided for when staff are unavailable and callers are asked to leave their name and number so that the SSSG can contact them.

**If you have found this information booklet useful, perhaps you would consider sending us a donation to continue our work, via BmyCharity on our website
www.stickler.org.uk**

16.4. HOW THE SSSG CAN HELP THE PATIENT

- By stressing in our literature, and to all professional and family contacts, that prompt treatment for retinal detachment and other eye problems associated with the condition can help to preserve vision.
- Encouraging them to seek help immediately if they experience any changes in vision.
- Encouraging them to seek genetic counselling and make reproductive choices based on sound knowledge
- By helping to alleviate feelings of isolation and distress in affected individuals and families throughout the UK, especially when they are undergoing medical procedures related to Stickler syndrome.
- By organising members days, workshops and conferences for affected families and for professionals who want to be informed about the condition.
- By issuing new members with a Tip Sheet about living with Stickler Syndrome, and a credit card size 'sight' card for them to present at casualty if they experience changes in vision.

17. REFERENCES AND PUBLICATIONS (SELECTED SECTION)

Stickler GB, Belau PG, Farrell FJ, et al. Hereditary progressive arthro-ophthalmopathy. Mayo Clinic Proceedings 1965; 40: 433-55

Stickler GB, Pugh DG. Hereditary progressive arthro-ophthalmopathy II . Additional observations on vertebral abnormalities, a hearing defect, and a report of a similar case. Mayo Clinic Proceedings 1967; 42: 495-500

Temple IK. Stickler's syndrome. J Med Genet 1989; 26:119-26

Snead MP, Payne SJ, Barton DE, et al. Stickler syndrome correlation between vitreoretinal phenotypes and linkage to COL2A1. Eye 1994; 8:609-14

Snead MP, Yates JR, Pope FM, Temple IK, Scott JD. Masked confirmation of linkage between type 1 congenital vitreous anomaly and COL2A1 in Stickler syndrome. Graefes Arch Clin Exp Ophthalmol 1996; 234: 720-1

Rai A, Wordsworth P, Coppock JS, Zaphiropoulos GC, Struther GR. Hereditary arthro-ophthalmopathy (Stickler syndrome): A diagnosis to consider in familial premature osteoarthritis. Br. J Rheumatol 1994; 33: 1175-80

Grahame R. Hypermobility Syndrome, Reports on Rheumatic Disease (series2). Arthritis and Rheumatism . Sept 1993 no 25

Beal RK. Hereditary arthro-ophthalmopathy (The Stickler syndrome). Report of a kindred with protrusio aceabuli. Cl;in Orthop 1977; 125:32-5

Richards AJ, Yates JR, Williams R, et al. A Family with Stickler syndrome Type 2 has a mutation in the COL1A1 gene resulting in substitution of glycine 97 caline in alpha 1(X1) collagen. *Hum Mol Genet* 1996, 5: 1339-43

Martin S, Richard AJ, Yates JRW, Pope FM, Scott JD, Snead MP. Stickler Syndrome Types 1 and 2: Confirmation of genetic heterogeneity and evidence for another locus. Presentation XX1 Meeting Club Jules Gonin 1998: A34

Pihajamaa T, Prockop DJ, Faber J, et al. Heterozygous glycine substitution in the COL11A2 gene in the original patient with the Weissenbacher—Zweymuller syndrome demonstrates its identity with heterozygous OSMED (nonocular Stickler Syndrome). *Am J Med Genet* 1998; 80:115-20

Snead MP, Yates John RW. Clinical and molecular genetics of Stickler Syndrome. *J of Medic Genet*. May 1999; 36 no 5: 353-359

Stickler GB, Hughes W, Houchin P. Clinical Features of Hereditary progressive arthro-ophthalmopathy (Stickler Syndrome): A Survey. *Genetic in medicine*; May/June 2001; vol 3 no 3: 192-196

Richard AJ, Martin S, Yates JRW, Scott JD, Baguley DM, Pope FM, Snead MP. COL2A1 exon mutations: relevance to the Stickler and Wagner syndromes. *Br J of Ophthol* ; April 2001, vol 84, no 4: 364-371

Houdayer, et al. Pierre Robin Sequence. *Amer. J of Med Genet* 2001, 15, 102:219-26

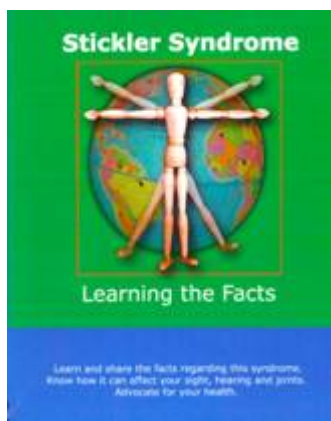
Rose et al. The hip in Stickler Syndrome. *J of Paed Ortho* 2001, 21: 657-663

Rose et al. Thoraco-lumbar Spinal Abnormalities in Stickler Syndrome. *Spine* 2001. 26. 4: 403-409

Rose et al Stickler Syndrome: Clinical Characteristics and Diagnostic Criteria. *Amer J of Med Gen* 138A: 199-207 2005

Richards, Laidlaw, Whittaker, Treacy, Rai, Bearcroft, Baguley, Poulson, Ang, Scott, Snead. High Efficiency of Mutation Detection in Type 1 Stickler Syndrome Using a Two-Stage Approach: Vitreoretinal Assessment Coupled with Exon Sequencing for Screening COL2A1: *Hum. Mutat*: 27(7): 696-704.

THE FIRST DVD ON STICKLER SYNDROME



STICKLER SYNDROME: LEARNING THE FACTS is the first in a series of three DVDs that will provide practical information to those living with Stickler Syndrome and health-care professionals. Stickler Syndrome is a progressive disorder due to a genetic malfunction of the connective tissue found in bones, eyes, ears and the face. Stickler Syndrome is believed to be the most common autosomal dominant inherited syndrome in the

UK, Europe and the United States. It is often under-diagnosed because the collection of symptoms is frequently not linked together. This film brings together the experiences and knowledge of health-care professionals and people living with the syndrome from the United Kingdom, Canada, and the United States.

This film was made possible through the assistance of the Tides Canada Foundation, Sage Centre, over 100 private donors, by those who participated, the Stickler Syndrome Support Group (SSSG) and Stickler Involved People (SIP).

**29 minutes: Region 2
£10.00 post free**

Please send me..... copy(ies) of the DVD Stickler Syndrome: Learning The Facts. I enclose a cheque for..... made payable to Stickler Syndrome Charitable Trust.

Please Print:

Name.....

...

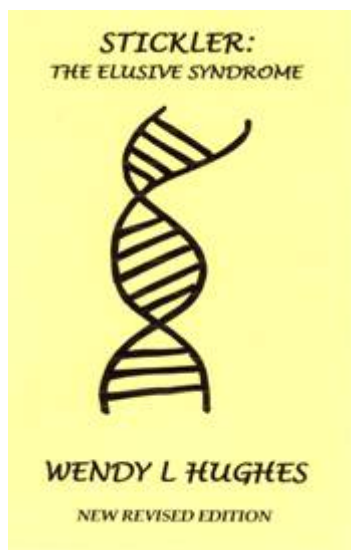
Address.....

.....

.....

Please send payment and completed form to: Stickler Syndrome Support Group, PO Box 3351, LITTLEHAMPTON, BN16 9GB

NEW REVISED EDITION
STILL THE ONLY BOOK ON THE DISORDER



STICKLER: THE ELUSIVE SYNDROME:

This new edition explains from a layperson's viewpoint, what Stickler Syndrome is, its genetic implications, its basic medical manifestations, and how it can affect the individual. The book, divided into three parts, provides sound advice by the author, a fellow sufferer, on how to cope with the condition. It includes topics such as other health issues, emotional and social issues as well as a chapter on coping with babies through to adolescence. It also includes a biographical sketch of Dr Gunner B Stickler who defined

the condition that bears his name, and how and The Stickler Syndrome Support Group was founded and has expanded. The final section tells the author's own story of living and coping with the condition, includes other families' experiences, and ends with some inspirational words from another fellow sufferer. This edition, is 50% larger than the first, and also includes some excellent medical colour illustrations and photographs of the author and her family, and those of other families who were willing to share their stories.

304 pages – 37 in colour
£19.99 post free

Please send me..... copy(ies) of the new edition of Stickler: The Elusive Syndrome. I enclose a cheque for.....made payable to Stickler Syndrome Charitable Trust.

Please Print

Name.....

Address.....

.....

.....

Please send payment and completed form to: Stickler Syndrome Support Group, PO Box 3351, LITTLEHAMPTON, BN16 9GB

18. HOW YOU CAN REACH US

Write to:

**Stickler Syndrome Support Group
PO Box 3351
LITTLEHAMPTON
BN16 9GB**

Telephone:

01903 785771

Email:

info@stickler.org.uk

Visit our website:

www.stickler.org.uk



© Wendy Hughes and The Stickler Syndrome Support Group 2006. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, without permission

Registered Charity No: 1060421