STICKLER SYNDROME

CLAIR A. FRANCOMANO

Adult Genetics, Harvey Institute for Human Genetics, Greater Baltimore Medical Center, Baltimore, Maryland

Stickler syndrome, also known as hereditary progressive arthro-ophthalmopathy, is a genetically heterogenous connective tissue disorder affecting the ocular, orofacial, and skeletal systems. Progressive myopia begins in the first decade of life and affected persons exhibit premature degenerative changes in various joints with slight hypermobility. Midface hypoplasia is usually evident in early life, and affected persons may demonstrate cleft palate or bifid uvula. Sensorineural hearing loss is a variable feature of the syndrome and may be progressive. Changes in four different collagen genes have been found to lead to these features.

INTRODUCTION

Stickler syndrome, also called hereditary progressive arthro-ophthalmopathy, is an autosomal dominant connective tissue disorder primarily affecting the ocular, orofacial, and skeletal systems (Stickler et al., 1965; Rimoin and Lachman, 1993) (Fig. 52.1). Stickler and colleagues first described the condition in two reports. The first paper (Stickler et al., 1965) described a new dominant syndrome consisting of progressive myopia beginning in the first decade of life and resulting in retinal detachment and blindness. Affected persons also exhibited premature degenerative joint disease with a mild epiphyseal dysplasia and joint hypermobility. In the second paper, Stickler and Pugh (1967) described changes in the vertebrae and hearing deficit as part of the syndrome, as well as the midface hypoplasia that is characteristic of the phenotype (Fig. 52.2). Opitz et al. (1972) reported that individuals with Stickler syndrome may also have features of Pierre Robin sequence. Phenotypic variability, both inter- and intrafamilial, is a hallmark of this syndrome. Mutations in four different collagen genes may cause the phenotype.

Incidence

Herrmann et al. (1975) suggested that Stickler syndrome is the most common autosomal dominant connective tissue disorder in the North American Midwest. Although estimates vary, it is thought that the frequency of Stickler syndrome is roughly 1/10,000 in the Caucasian population of the United States. Phenotypic variability of the syndrome can make the diagnosis difficult, and the syndrome may be significantly underdiagnosed.

Although chronic musculoskeletal pain, retinal detachments, and hearing loss may significantly impact quality of life, longevity is not affected by this disorder.

Diagnostic Criteria

The major systems involved in Stickler syndrome are the ocular, auditory, orofacial, and musculoskeletal systems. Severe myopia with onset in the first decade of life, vitreous degeneration, spontaneous retinal detachment, chorioretinal degeneration, open angle glaucoma, and presenile cataracts are the ocular features of the disorder (Stickler et al., 1965; Rimoin and Lachman, 1993; Liberfarb et al., 2003). During early childhood, midface hypoplasia is often evident and becomes less pronounced with age in persons with COL2A1 mutations. Pierre Robin sequence (see Chapter 46), bifid uvula, and/or cleft palate may be present and result in feeding and respiratory problems (Schreiner et al., 1973). Mixed and
sensorineural hearing loss in the higher frequencies is also a feature of the syndrome (Liberfarb and Goldblatt, 1986). In early life, joint pain and stiffness may signify the onset of juvenile osteoarthritis. Early-onset degenerative joint disease is a major complication in adulthood. Radiographs of the skeleton may demonstrate a mild form of spondyloepiphyseal dysplasia, even in individuals without other signs of the syndrome (Stickler and Pugh, 1967; Rimoin and Lachman, 1993) (Fig. 52.3). An early report suggested that mitral valve prolapse is present in 45% of the affected individuals (Liberfarb and Goldblatt, 1986). However, more recent reports (Ahmad et al., 2003; Donoso et al., 2003) found a much lower incidence of mitral valve prolapse among individuals with Stickler syndrome, and suggested that the incidence is comparable with that of the general population. This may reflect the change in diagnostic criteria for mitral valve prolapse published in 1988 (Levine et al., 1988), or a more strict definition of Stickler syndrome in the more recent publications.

Liberfarb et al. (2003) proposed a point system for establishing the diagnosis of Stickler syndrome. Two points are awarded for the presence of each of the following findings: cleft palate, vitreous degeneration or retinal detachment, and high-frequency sensorineural hearing loss. One point each is awarded for the characteristic facies, hypermobile tympanic membranes, a history of femoral head failure (severe delay in ossification), radiographically demonstrated osteoarthritis before age 40 years, spinal deformities, positive family history, and identification of a causative mutation.

![FIGURE 52.1](typical_stickler綜合.jpg) Typical Stickler syndrome. Affected boy (left) and his affected father (right). In addition to oro-auriculo-facial manifestations (see Fig. 52.2), affected individuals frequently present with ocular and musculoskeletal features.

![FIGURE 52.2](midface_hypoplasia.jpg) Midface hypoplasia in Stickler syndrome. A flat facial profile with depressed nasal bridge, midface, or maxillary hypoplasia, and micrognathia are often seen in Stickler syndrome. Other oro-auriculo-facial features may include epicanthal folds, clefting of the hard or soft palate, Pierre Robin sequence, sensorineural deafness, and dental anomalies.
A score of 5 is necessary to make the diagnosis of Stickler syndrome. Liberfarb et al. (2003) reported 25 subjects with molecular confirmation of COL2A1 mutations, all of whom satisfied these diagnostic criteria with a mean diagnostic score of 7.3 out of a possible 9.

**Etiology, Pathogenesis, and Genetics**

The observation that type II collagen is present in both cartilage and the secondary vitreous of the eye suggested that the basis of Stickler syndrome may be a defect in COL2A1, the gene that encodes type II collagen (Maumenee, 1979) (Table 52.1). Subsequently, Stickler syndrome was linked to the COL2A1 gene (Francomano et al., 1987; Knowlton et al., 1989; Snead et al., 1996). Since then, more than 82 dominant mutations in the COL2A1 gene have been identified in individuals or families with Stickler syndrome (Ahmad et al., 1991; Brown et al., 1995a; Liberfarb et al., 2003; Zechi-Ceide et al., 2008). With few exceptions, most of the mutations introduce a premature stop codon into the region of the gene encoding the triple helical domain of the collagen molecule.

*COL2A1* encodes a single procollagen monomer that assembles into a homotrimer with noncollagenous amino- and carboxy-terminal ends, beginning at the carboxy-terminal domain. These stable triple helices aggregate into the supramolecular structures of fibrillar collagen. The premature stop codons introduced by the mutations typical of Stickler syndrome essentially delete the carboxy-terminal region of the monomer, and so they are not able to participate in the assembly of the triple helical trimer. Moreover, nonsense-mediated RNA decay eliminates most of the prematurely terminated transcripts. Functionally, only half the normal number of collagen monomers is available to be incorporated into type II collagen trimers. It is hypothesized that this functional haploinsufficiency of type II collagen results in type 1 Stickler syndrome in most cases.

Genetic heterogeneity in Stickler syndrome was first demonstrated by the exclusion of linkage to COL2A1 in about 50% of families (Knowlton et al., 1989). Mutations in the COL11A2 gene are the most common cause of Stickler syndrome, but they are not associated with ocular features as severe as those with COL2A1 mutations. Therefore, individuals with Stickler syndrome as a result of a mutation in the COL11A2 gene would not be expected to manifest ocular anomalies as severe as those with Stickler syndrome because of mutations in COL2A1 and COL11A1.

**TABLE 52.1 Expression of Type II Collagen and Type XI Collagen in Cartilage and the Eye**

<table>
<thead>
<tr>
<th>Cartilage</th>
<th>Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>COL2A1</td>
<td>COL11A1</td>
</tr>
<tr>
<td>COL11A2</td>
<td>COL2A1</td>
</tr>
<tr>
<td>COL2A1</td>
<td>COL11A1</td>
</tr>
</tbody>
</table>

* Type II collagen is always a homotrimer of the product of the COL2A1 gene. In cartilage, type XI collagen is a heterotrimer of the products of the COL11A1, COL11A2, and COL2A1 genes. However, in the ocular vitreous, type XI collagen is a heterotrimer of the products of the COL11A1, COL5A2, and COL2A1 genes. Therefore, individuals with Stickler syndrome as a result of a mutation in the COL11A2 gene would not be expected to manifest ocular anomalies as severe as those with Stickler syndrome because of mutations in COL2A1 and COL11A1.
in the genes encoding type XI collagen (COL11A1 and COL11A2) have been identified in over 30 affected individuals to date (Vikkula et al., 1995; Richards et al., 1996; Majava et al., 2007). Clinical and molecular findings have suggested that the phenotype in Stickler syndrome families with severe ocular manifestations are the result of mutations in either COL2A1 or COL11A1, whereas the phenotype in families with milder or absent eye involvement results from mutations in the COL11A2 gene (Snead et al., 1994) (Table 52.1). Some Stickler syndrome families are not linked to COL2A1, COL11A1, or COL11A2, suggesting that at least a fourth gene is involved in the autosomal dominant form of the phenotype (Wilkin et al., 1998).

Characterization of the vitreoretinal phenotype in Stickler syndrome has resulted in a proposed classification of the syndrome into two subtypes with ocular involvement, type 1 and type 2, caused by mutations in COL2A1 and COL11A1, respectively, and type 3, or the “nonocular” type, caused by mutations in COL11A2 (Snead et al., 1996, 1996). Richards et al. (2006) described the vitreous in type 1 Stickler syndrome as characterized by a vestigial gel remnant in the retrorenal space, bounded by a highly folded membrane. This finding is present at birth and remains throughout life. According to Richards et al. (2006), type 2 Stickler syndrome also has abnormal vitreous architecture, although it is distributed throughout the entire posterior segment. In type 2 Stickler syndrome, there is decreased normal fibrillar gel matrix. The remaining gel matrix has gel strands of variable diameters, many of which are thickened, and have a beaded appearance (Snead et al., 1996). Individuals with type 2 Stickler syndrome often have milder ocular manifestations (Snead et al., 1994), and early-onset high myopia is not typically a feature (Vikkula et al., 1995). The COL11A2 gene is not expressed in the vitreous, and consequently mutations in COL11A2 cause a nonocular variant of Stickler syndrome, designated type 3.

Mutations in COL2A1 are associated with higher risk of retinal detachment, a lower likelihood of early-onset deafness, and a less characteristic facial appearance with aging, whereas COL11A1 mutations commonly cause early-onset deafness and are associated with the characteristic face even in adult life.

Stickler syndrome caused by mutations in COL2A1, COL11A1, or COL11A2 is inherited as an autosomal dominant disorder. Van Camp et al. (2006) reported an autosomal recessive form of Stickler syndrome caused by mutation in the COL9A1 gene. The authors note that the vitreous phenotype in individuals with this form did not resemble the membranous, beaded, or nonfibrillar phenotypes described in types 1, 2, and 3, but rather resembled an aged vitreous with progressive gel liquefaction. Of the four individuals reported by Van Camp et al. (2006), two had retinopathy and two had normal retinas. All four had high myopia and high-frequency hearing loss.

** Genetic counseling  **  Most cases of Stickler syndrome are familial. Those caused by mutations in the COL2A1, COL11A1, and COL11A2 genes have a 50% recurrence risk to offspring, in keeping with the autosomal dominant inheritance pattern. In families with autosomal recessive COL9A1 mutations, siblings of an affected person have a 25% risk, whereas the risk to offspring is extremely low.

** Diagnostic Testing  **

Diagnostic testing for Stickler syndrome is complicated by the known genetic heterogeneity. Richards et al. (2006) suggested that an efficient strategy for molecular diagnosis was a two-stage approach including vitreoretinal assessment followed by sequence analysis of COL2A1 in those individuals with the typical eye findings for type 1 Stickler syndrome. Others have suggested that the vitreoretinal findings are not entirely specific and that the typical ocular findings of type 1 Stickler syndrome may also be seen in individuals with COL11A1 mutations (Majava et al., 2007). Testing is currently available through a small number of clinical laboratories worldwide.

** Differential Diagnosis  **

Wagner syndrome, Marshall syndrome, and the Weissenbacher-Zweymuller syndrome are often confused with Stickler syndrome. Historically, there has been a debate between “lumpers” and “splitters” as to whether the disorders are phenotypic variants of the same syndrome or distinct phenotypic entities.

Wagner (1938) reported a family with 28 members affected by low myopia (~3.00 diopters or less), a fluid vitreous, and cortical cataracts. No extraocular features were described. This syndrome has come to be called Wagner syndrome, hyaloidetinal degeneration of Wagner, Wagner vitreoretinal degeneration, or erosive vitreoretinopathy. Affected individuals manifest complete absence of the normal vitreal scaffolding and preretinal, equatorial, and avascular grayish-white membranes. Retinal detachment was not noted in any of the 28 members of the original Swiss family studied by Wagner (1938). Schwartz et al. (1989) suggested that Wagner syndrome is characterized by vitreoretinal degeneration without extraocular manifestations, whereas Stickler syndrome also has extraocular manifestations in the musculoskeletal and craniofacial systems.

Fryer et al. (1990) studied a large family with Wagner syndrome. Affected individuals in this family had none of the extraocular features associated with Stickler syndrome. The COL2A1 locus was excluded as the site of the mutation. Brown et al. 1995b demonstrated linkage of the original Wagner syndrome family to a locus on chromosome 5q13-14. However, the demonstration by Korkko et al. (1993) of a COL2A1 mutation in a family with Wagner syndrome
indicates that there are at least two loci causing Wagner syndrome. Affected individuals in this family had early-onset cataracts, lattice degeneration of the retina, and retinal detachment.

Marshall syndrome is a rare autosomal dominant skeletal dysplasia characterized by ocular abnormalities, sensorineural hearing loss, craniofacial anomalies, and anhidrotic ectodermal dysplasia (Marshall, 1958). Affected individuals are myopic (ranging from −3 to −20 dioptries) with a fluid vitreous and congenital cataracts. Retinal detachment is reported. Craniofacial characteristics are common. Micrognathia is evident in some affected individuals, as is the absence of nasal bones, producing a short nose with a very flat nasal bridge, anteverted nares, and a long philtrum.

The distinction between the Stickler and Marshall syndromes is supported by the work of Ayme and Preus (1984) who surveyed published reports on the two syndromes. A set of 18 affected individuals with clinical description, photographs, and radiographs was used to tabulate a list of 53 features, including facial characteristics, size and habitus, and joint, limb, and hip manifestations. Analysis of these features revealed two distinct groups of individuals. The authors concluded that there was no reason not to consider these two syndromes as separate disorders. The authors suggested that the facies of individuals with the two disorders differ. Those with Marshall syndrome have a flat or retruded midface, whereas those with Stickler syndrome have a flat malar area, which is often erroneously described as a flat midface. In Marshall syndrome, there are thick calvaria, abnormal frontal sinuses, and intracranial calcifications, and the globes of the eye appear large, possibly because of a shallow orbit.

In affected members of a large kindred diagnosed with Marshall syndrome, Griffith et al. (1998) identified a mutation in the COL11A1 gene. The results demonstrate that both Marshall syndrome and a subset of Stickler syndrome families have mutations in the COL11A1 gene. Majava et al. (2007) described 10 previously unreported individuals with heterozygous mutations in COL11A1. In 4 of the 10, the phenotype was felt to be Marshall syndrome because of characteristic facial features and severe early-onset hearing loss; all 4 had a splice-site mutation in intron 50 of COL11A1. All of the remaining individuals (6/10) had a phenotype overlapping between Marshall and Stickler syndromes, with less pronounced facial features. None of these less severely affected individuals had splice-site mutations in exon 50. Thus, it appears that there are at least some people in whom the distinction between Marshall and Stickler syndrome is very difficult to make on clinical or molecular grounds.

Weissenbacher and Zweymueller (1964) described an infant with Pierre Robin sequence (see Chapter 46) and chondrodysplasia. Their eponymous syndrome is characterized by neonatal micrognathia and rhizomelic chondrodysplasia with dumbbell-shaped femora and humeri, and regression of bone changes and normal growth in later years (Weissenbacher and Zweymueller, 1964; Haller et al., 1975). Radiologically there are also vertebral coronal clefts. Average growth after 2–3 years, “catching up” to average height, is seen.

It has been suggested that Weissenbacher-Zweymueller syndrome may represent a neonatal expression of Stickler syndrome (Kelly et al., 1982). Ayme and Preus (1984) did a cluster analysis of published cases and concluded that Weissenbacher-Zweymueller syndrome and Stickler syndrome are separate entities. Among the features found in Weissenbacher-Zweymueller syndrome but not in Stickler syndrome were markedly decreased body length at birth with short limbs, catch-up growth after 2 or 3 years, lack of progressive deformity, and autosomal recessive inheritance as indicated by affected siblings with phenotypically normal parents. Myopia and retinal detachment are characteristics of Stickler syndrome that are not found in Weissenbacher-Zweymueller syndrome. However, in 1998, the person originally described with this syndrome was found to have a mutation in COL11A2, demonstrating that Weissenbacher-Zweymueller syndrome is at least allelic to a subset of “nonocular” Stickler syndrome (Pihlajamaa et al., 1998).

**MANIFESTATIONS AND MANAGEMENT**

Optimal management of Stickler syndrome requires an interdisciplinary team of specialists, tailored to the affected individual’s specific medical needs.

**Growth and Feeding**

These are not an issue in Stickler syndrome except in those babies with cleft palate, which makes it difficult for the baby to suck forcefully enough to draw milk through a nipple, causing feeding difficulties. It is possible to breastfeed some infants with cleft palate, though this will require extra patience and is more likely to be successful in babies with less severe clefts. There is an excellent summary of the feeding difficulties that may be seen in babies with Stickler syndrome who manifest the Robin phenotype in Chapter 46.

**Evaluation**

- Babies with Stickler syndrome who have a cleft palate should be monitored for inadequate nutrition by frequent plotting of height and weight attainment, as for all babies with cleft palate.
- A feeding evaluation by an occupational or physical therapist is recommended for any baby with difficulty feeding.
Treatment

- During bottle feeding, the baby with a cleft palate should be in a sitting position to help prevent milk from leaking into the nose through the cleft.
- A regular nipple designed for premature babies and a squeeze bottle can help a baby with cleft palate feed more easily.
- Occasionally, a baby may feed best with the aid of a plastic artificial palate, called an obturator, which temporarily covers a palatal cleft. Not all cleft palate teams favor this approach.
- Most cleft palate teams pay close attention to feeding and help parents establish good feeding practices right after the child is born.
- Aggressive management of obstructive airway complications seen in Robin syndrome is essential, including for prevention of feeding problems (see Chapter 46).

Development and Behavior

Both motor and cognitive development are normal in Stickler syndrome. Children with high myopia or significant hearing difficulties will require classroom accommodations. It is important to recognize these sensory deficits early and obtain the necessary visual or auditory aids to facilitate optimal early childhood learning.

Ophthalmologic

Major manifestations of the ocular system in Stickler syndrome include moderate to severe myopia (at least –5 diopters) of childhood onset, spontaneous retinal detachment, and a congenital vitreous anomaly. Minor manifestations include presenile cataract, glaucoma, and strabismus. Early-onset high myopia can lead to spontaneous retinal degeneration and detachment. Refractive errors, cataracts, and vitreoretinal abnormalities may be detected early in life in individuals with Stickler syndrome (Wilson et al., 1996).

Seery et al. (1990) found cataracts of various types or aphakia in 115 of 231 eyes of individuals with Stickler syndrome. The most frequent and distinctive lesions, described as wedge and fleck cataracts, accounted for 40 of the 93 cataracts observed.

Stickler et al. (2001), in a survey of 316 individuals self-identified as having Stickler syndrome, found that 95% reported eye pathology of some sort, including a history of retinal detachment in 60%, myopia in 90%, and blindness in 4%.

Evaluation

- Frequent (at least annual) examinations by an ophthalmologist are recommended, starting in infancy, to evaluate the severity of myopia, strabismus, the vitreoretinal architecture, and the presence or absence of cataracts and glaucoma.

Treatment

- Corrective lenses should be prescribed for myopia as early as possible.
- Prophylactic laser photocoagulation of vitreoretinopathy should be considered. Leiba et al. (1996) retrospectively reviewed a large family with Stickler syndrome (at least 42 affected members). Ten eyes were prophylactically treated with laser photoagulation. In this family, the incidence of retinal detachment was significantly higher in nonlased eyes than in lased eyes. Ang et al. (2008) reported on a retrospective analysis of prophylaxis for retinal detachment using cryotherapy. Sixty-two individuals received bilateral prophylactic cryotherapy; five (8%) required further procedures during the follow-up period (mean of 11.5 years). Of 31 individuals who received unilateral prophylaxis after a retinal detachment in the contralateral eye, 3 (10%) experienced retinal detachment during the follow-up period. The authors speculate that people with Stickler syndrome who suffered a previous retinal detachment may be at higher risk for another detachment in the opposite eye, compared with those who never experienced a retinal detachment.
- Surgical interventions to repair retinal detachments or tears, or to correct cataracts, glaucoma, or strabismus, are performed as they would be for persons without Stickler syndrome, using either primary vitrectomy or scleral buckling. Abeysiri et al. (2007) reported on the outcomes of surgery for retinal detachment in people with Stickler syndrome. They found that the primary reattachment rate was higher (84.2%) for primary vitrectomy compared with 67% for scleral-buckle surgery. Because complications were more commonly seen in those with re-detachment and multiple surgeries, these authors suggest that primary vitrectomy is the procedure of choice for individuals with Stickler syndrome who have experienced retinal detachment.

Craniofacial

Major manifestations of the oro-auriculo-facial system in Stickler syndrome include cleft palate with or without the other features of Robin sequence. Minor manifestations include midface hypoplasia, micrognathia, and sensorineural hearing loss in the higher frequencies. Stickler et al. (2001) found that 41% of the 316 respondents (129 people) to their survey had a cleft palate. Seventy-five of these had been diagnosed at birth with Robin sequence.
A retrospective review of 90 children with Robin sequence was carried out using oximetry, apnea monitoring, and sleep studies to identify subgroups at a higher risk of developing severe airway obstruction, and response to treatment was assessed (Tomaski et al., 1995). Airway obstruction and feeding difficulties vary among children with Robin sequence. Treatment is challenging and the appropriate management may not be readily identified, causing delay in securing the airway. Although most children with Stickler syndrome do not suffer from debilitating airway and feeding difficulties, all babies with cleft palate or Robin sequence do have some feeding difficulties, with the severity proportional to the degree of airway obstruction (Tomaski et al., 1995; Stickler et al., 2001). (See Growth and Feeding above as well as Chapter 46 for a more detailed description of management of Robin sequence.)

Babies with cleft palate are especially susceptible to middle ear disease. The cleft can contribute to recurrent otitis media, which may lead to mild or moderate hearing loss. If properly treated in infancy and childhood, the hearing losses need not be permanent. If not properly managed, speech development may be affected and hearing loss may become permanent. Ear disease usually improves following cleft palate repair.

Some children with cleft palate may develop speech more slowly than other children. Their words may sound nasal and they may have difficulty producing some consonant sounds. However, after cleft palate repair, most children eventually catch up and develop normal speech, though some will require speech therapy.

### Evaluation

- Otolaryngology evaluation should be done for all individuals with Stickler at diagnosis, especially to evaluate the affected individual for ear and palate abnormalities, including bifid uvula and submucous cleft palate. An otolaryngologist should examine all babies with cleft palate within the first 3–6 months of life.
- Hearing should be tested regularly in babies and children with cleft palate. Audiograms should be done at regular intervals to monitor mixed and sensorineural hearing loss.
- Speech and swallow evaluations should be accomplished for all affected individuals with clefts.

### Treatment

- Otitis media is treated with antibiotics and, if recurrent, ventilation tubes, as would be done for any child without Stickler syndrome.
- The timing and type of surgery for cleft palate will depend on a number of factors, including the preference of the individual surgeon, the general health of the baby, and the nature of the cleft. Cleft palate repair is generally timed to restore the partition between the nose and mouth as early as possible, usually between 12 and 18 months.
- Hearing aids may be required. Devices to help children hear in school may be beneficial when hearing loss is documented, as may preferential classroom placement.
- Speech therapy will almost always be needed in children with clefts.

### Ears and Hearing

High-frequency sensorineural hearing loss is a frequent manifestation in Stickler syndrome, and ranges from mild to severe. Hearing loss may be progressive during adulthood and may be compounded by conductive hearing loss related to recurrent otitis and cleft palate.

### Evaluation

- Audiometry is a standard evaluation as part of the diagnostic process for Stickler syndrome. All children affected by Stickler syndrome should have a hearing test. Affected adults should be aware that hearing loss may progress in adulthood and have a low threshold for repeat testing if hearing loss is suspected.

### Treatment

- Treatment for hearing loss is determined by the severity and type of deafness. Options include hearing aids and vibrotactile devices; cochlear implants are considered in children over the age of 12 months with severe to profound deafness.
- If hearing loss is prelingual, optimal management is crucial for optimal cognitive development.

### Musculoskeletal

Major manifestations of the musculoskeletal system in Stickler syndrome include early-onset degenerative joint disease and radiographic evidence of a mild spondyloepiphyseal dysplasia. Minor manifestations include joint hypermobility, including hyperextensibility of the knees and elbows; joint pain or stiffness in childhood; arachnodactyly; scoliosis; and Marfanoid habitus. The joint hyperflexibility of youth usually evolves into degenerative arthritis. The musculoskeletal manifestations can be extremely variable both within and between families. Radiographic manifestations are often very mild and are infrequently reported.

Osteoarthritis, with onset as early as the third decade of life, is one of the major manifestations of Stickler syndrome.
Severe osteoarthritis with an early onset has been associated with mutations in the COL2A1 gene (Ritvaniemi et al., 1995). Radiographs show evidence of a mild spondyloepiphyseal dysplasia. A specific COL2A1 mutation (Arg519Cys) has been identified in at least five unrelated families with early-onset osteoarthritis associated with mild spondyloepiphyseal dysplasia. Spondyloepiphyseal dysplasia is characterized by typical skeletal changes, including delayed ossification of the axial skeleton with ovoid vertebral bodies. With time, the vertebral bodies appear flattened. There is delayed ossification of the femoral heads, pubic bones, and calcaneus (heel). Coxa vara (deformity of the hip joint) is common.

Evaluation

- Individuals with Stickler syndrome should have a full musculoskeletal examination to determine the involvement of the skeleton in the phenotype. Orthopedic problems, spinal column instability, deformities of the legs, arthrosis of the hips, and other skeletal manifestations can then be identified and appropriate treatment planned.
- Rheumatology consultation may be helpful to determine severity and management of osteoarthritis.
- Rehabilitation medicine or physical therapy consultation may be indicated to evaluate body mechanics and range of motion and strength, and to recommend strengthening exercises.
- Radiographic skeletal survey in childhood is suggested to document the presence and severity of spondyloepiphyseal dysplasia and other orthopedic abnormalities.
- If chronic pain is present, evaluation by a pain specialist may be helpful.
- Occupational therapy evaluation is indicated if there is concern about the affected individual’s ability to function in daily activities.

Treatment

- Aggressive pain management may significantly enhance quality of life and should be prescribed as needed. A pain specialist may be helpful in this regard.
- Splints may be required for strength and to stabilize lax joints, particularly during sports.
- Aids or braces may be required to assist in daily activities.
- Education of the affected individual and family regarding joint protection is important.
- Education of the affected individual regarding exercises for strengthening muscles around lax joints is recommended.
- Hydrotherapy, or other physical therapy modalities, may increase range of motion, endurance, and strength.
- An individual exercise program should be developed, such as one recommended by the rehabilitation medicine or physical therapy evaluation.

Cardiovascular

Among 57 individuals with Stickler syndrome, Liberfarb and Goldblatt (1986) found that 50% of females and 43% of males had mitral valve prolapse. More recent publications suggest that mitral valve prolapse may not be any more frequent in Stickler syndrome than it is in the general population (Ahmad et al., 2003).

Evaluation

- Echocardiogram should be performed only if there is reason to suspect mitral valve prolapse based on clinical findings.

Treatment

- Antibiotic prophylaxis for subacute bacterial endocarditis was formerly recommended for all individuals with mitral valve prolapse. However, new guidelines from the American Heart Association in 2007 state that in most cases antibiotic prophylaxis is not necessary for persons with mitral valve prolapse or mitral regurgitation.
- β-Blockade may be used for symptomatic mitral valve prolapse.

ACKNOWLEDGMENTS

Previous editions of this chapter were co-authored by Drs. Douglas Wilkin and Ruth Liberfarb. Their contributions to this work are gratefully acknowledged.

RESOURCES

Support Organizations

Stickler involved People (SIP)
15 Angelina
Augusta, KS 67010, USA
Telephone: (316) 259-5194
Email: sip@sticklers.org
Web site: www.sticklers.org/sip/
England
Stickler Syndrome Support Group
P.O. Box 371
Walton on Thames
Surrey, KT12 2YS, UK

leaves the reader with hope and skills to manage Stickler problems in layman terms. The approach is positive and

REFERENCES

March of Dimes: Cleft lip and palate

Website: http://www.marchofdimes.com/pnhec/4439_1210.asp

REFERENCES


STICKLER SYNDROME


