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Thoracolumbar Spinal Abnormalities in Stickler Syndrome

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Study Design: Retrospective review of clinical and radiographic records of patients with Stickler syndrome.

Objectives: To describe thoracolumbar spinal abnormalities and their correlation with age and back pain among patients with Stickler syndrome.

Summary of Background Data: Stickler syndrome (hereditary arthro-ophthalmopathy) is an autosomal dominant connective tissue disorder characterized by skeletal, ocular, oral–facial, cardiac, and auditory manifestations. Prevalence is approximately 1 in 10,000 (similar to that of Marfan syndrome). No one has investigated spinal abnormalities in a large series of patients.

Methods: A single-center evaluation of 53 patients from 24 families with Stickler syndrome (age range, 1–70 years) in a multidisciplinary genetics clinic. Thoracolumbar radiographs were analyzed for spinal abnormalities and correlation with age and back pain.

Results: Thirty-four percent of patients had scoliosis, 74% endplate abnormalities, 64% Schmorl's nodes, 43% platyspondylia, and 43% Scheuermann-like kyphosis. Sixty-seven percent of patients and 85% of adults reported chronic back pain. Endplate abnormalities and Schmorl's nodes were associated with adult age; endplate abnormalities, Schmorl's nodes, and adult age were associated with back pain. Only one adult patient was free of spinal abnormalities.

Conclusions: Spinal abnormalities are nearly uniformly observed in Stickler syndrome, progress with age, and are associated with back pain. Although common, scoliosis is generally self-limited (only one patient needed surgical treatment). Correct diagnosis of this syndrome facilitates early identification and management of other potentially severe systemic manifestations and genetic counseling for affected families. Moreover, recognition of Stickler syndrome allows accurate prognosis for skeletal abnormalities and anticipation of potential surgical complications. [Key Words: arthro-ophthalmopathy, back pain, connective tissue dysplasia, kyphosis, scoliosis]
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Stickler syndrome (hereditary arthro-ophthalmopathy) is an autosomal dominant connective tissue disorder linked to mutations in Types II and XI collagen. Exact incidence is unknown but is thought to be at least 1 in 10,000, slightly more common than Marfan syndrome.[10,13,21] The disorder was first recognized by Stickler et al[30] in a family with midface hypoplasia, hearing loss, retinal degeneration, joint hypermobility, and premature osteoarthritis. Subsequent reports have expanded details of inheritance, phenotype, and molecular defects and have highlighted the extreme clinical variability of the syndrome.[10,15,16,21,22,24,31,33,36]

Genetic studies initially linked Stickler syndrome with *COL2A1*, the gene encoding type II collagen.[1,7,12] Subsequent studies have identified linkage to and specific mutations in *COL2A1*, *COL11A1*, and *COL11A2*.[18,25,32,35] Type II collagen is a homotrimer of three *COL2A1* gene products, whereas type XI collagen is a heterotrimer containing one each of the *COL2A1*, *COL11A1*, and *COL11A2* gene products.[4] Further genetic heterogeneity is likely because linkage to all three genes has been excluded in some affected families.[18]

Patients are typically recognized by the presence of midface abnormalities and ocular manifestations.[15,16,22,30] Approximately 25% have cleft palate, which may appear as the life-threatening Pierre–Robin syndrome at birth.[15,16,22] Other dysmorphic facial features include malar hypoplasia, enophthalmos, micro/retrognathia, and dental abnormalities. Figure 1 shows typical facial profiles in three generations of affected relatives with a known *COL2A1* single base pair deletion. The features are most apparent in young individuals and lessen with age. High myopia with vitreous degeneration and predisposition to retinal detachment develops in early childhood.[19,27] High-frequency sensorineural hearing loss progresses with age,[15,16] and mitral valve prolapse is a feature.[17] Pectus excavatum and carinatum are frequently observed.[22] No cognitive limitations are associated with the syndrome.

Approximately 80% of patients with Stickler syndrome have musculoskeletal manifestations.[14,15,16,22,29,30] Features include thin extremities with relative muscle hypoplasia (often described as similar to a Marfanoid habitus, although height is generally normal).[30,33] Weingeist et al[33] found radiographic evidence of spondyloepiphyseal dysplasia in all 16 patients they reported, and Spallone[27] found similar results in all 12 patients studied. Articular hypermobility is present

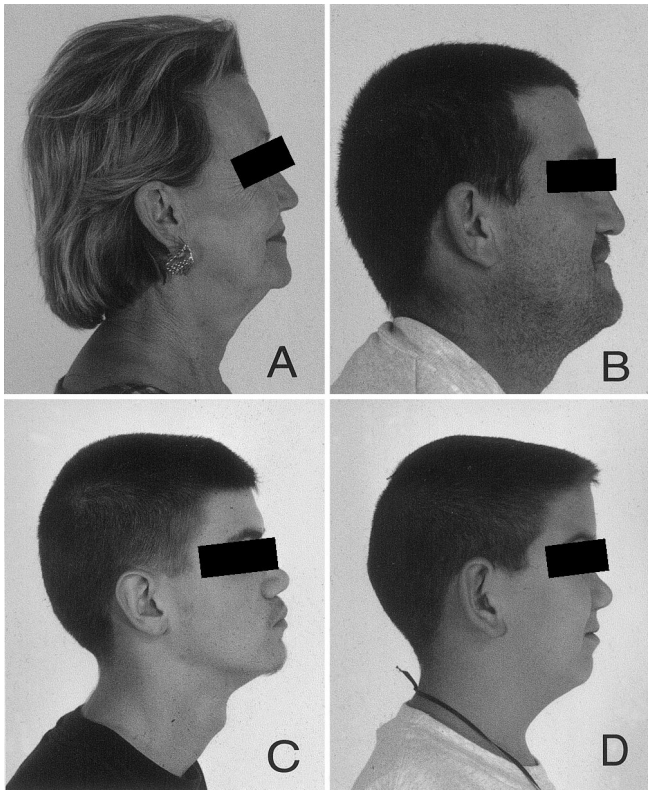

Figure 1. Facial profiles of three generations of affected relatives demonstrate typical facial manifestations of midface hypoplasia, micro/retrognathia, enophthalmos, and hypoplastic alae. Pictured are grandmother (age 55), son (age 37), and grandsons (age 13 and 9). Phenotype varies from mildly affected grandmother (**A**) to son (**D**) with Pierre–Robin syndrome at birth.

and often leads to instability, subluxation, or dislocation.[10,14,16,30] Progressive large-joint osteoarthritis may begin in the teenage years and frequently results in physical disability.[10,14,22,23,29,30] Total joint arthroplasty is common and may be necessary before age 20.[29] Specific hip manifestations include protrusio acetabuli,[2] coxa valga,[3,10] and Legg–Perthes–like disease or slipped epiphysis.[3,20] Anecdotal reports indicate that osteoporosis may be common in Stickler syndrome, but this has not been systematically evaluated.

Reported spinal abnormalities include spondylolisthesis,[14] scoliosis,[10,13,16,30,31] hyperkyphosis, and Scheuermann-like kyphosis.[10,22,30] Stickler[30] recognized spinal abnormalities in his initial descriptions of the syndrome. Liberfarb et al[15] reported scoliosis in 11 of 70 patients based on physical examination but did not further characterize vertebral findings. Letts et al[13] reported specifically on spinal abnormalities in the syndrome but these observations were limited to a group of seven children without information on back pain.

This is a report of the first systematic examination of the prevalence and severity of thoracolumbar spinal abnormalities and back pain in a large number of patients with Stickler syndrome.

Table 1. Diagnostic Criteria for Stickler Syndrome

Major	Minor
Vitreoretinal degeneration[1]	Myopia ≥ -5 diopters
Cleft palate/bifid uvula	Degenerative joint disease onset $\leq$ 40 years
High frequency hearing loss[2]	Joint laxity
Typical hip anomaly[3]	Typical facies[4]
	Positive family history[5]

Diagnostic criteria for Stickler syndrome used in this study. All patients met at least three criteria with at least one major manifestation. These are not validated for the diagnosis of Stickler syndrome but are under evaluation for this purpose.
[1] Includes juvenile vitreous degeneration and spontaneous retinal detachment.
[2] Threshold $\geq$ 40 db at 6 khz.
[3] Slipped capital femoral epiphysis or Legg–Perthes like disease.
[4] Malar hypoplasia, enophthalmos, flat facial profile, micro/retrognathia.
[5] At least one first degree relative who independently meets diagnostic criteria in a pattern consistent with autosomal dominant inheritance.

■ Methods

Radiographic and clinical data were reviewed in 58 consecutive patients from 24 families with Stickler syndrome seen at the National Institutes of Health Medical Genetics Clinic over a 24-month period from 1997 through 1999. Patients were enrolled (with written informed consent) in a natural history and molecular etiology study approved by the National Institutes of Health National Human Genome Research Institute Institutional Review Board (protocol 97-HG-0089). The patients pictured in Figure 1 provided written informed consent for publication of unmasked facial photographs for this publication.

All patients were examined by one or more medical geneticists experienced in diagnosing Stickler syndrome and related connective tissue disorders (HPL, RML, CAF). No formal diagnostic criteria have been established for Stickler syndrome. All patients included in this study manifested three or more Stickler-associated features, at least one of which was considered major (Table 1). Mitral valve prolapse was not used as a diagnostic criterion because in the authors' experience it lacks specificity among heritable disorders of connective tissue.

Standing anteroposterior and lateral vertebral radiographs were prospectively obtained in 53 patients. The 5 patients without radiographs were all 3 years of age or less at the time of evaluation, and radiographs were deferred because of age. In the majority of cases the spine was imaged in three sections (cervical, thoracic, and lumbosacral) rather than with single full-spine images, because of equipment limitations. Data on back pain were obtained from medical records, standardized pain inventories, and personal interview from patients aged more than 5 years. Patients were asked to describe pain in the neck and upper and lower back and to report the chronicity of the pain. No patients had back pain referable to spinal trauma. For the purposes of this study, chronic back pain was defined as pain in the upper or lower back (but not neck) occurring at least daily for a minimum of 6 months.

All radiographs were jointly read by two orthopedic surgeons with experience in spinal surgery (NUA, UMA). These observers were blinded to the presence of back pain. All vertebral angular measurements were made with the technique of Cobb.[5] Scoliosis was defined as curvature greater than 10°, and curve patterns were described using King's classification.[11] Abnormal kyphosis was determined using the age- and sex-adjusted normal ranges described by Fon et al.[6] Scheuermann-

Table 2. Thoracolumbar Abnormalities by Patient Age

	Total (n = 53)	Pediatric Patients (n = 18)	Adult Patients (n = 35)	Pediatric *vs.* Adult
Scoliosis	18 (34%)	6 (33%)	12 (34%)	$P = 0.94$
Endplate abnormalities	39 (74%)	6 (33%)	33 (94%)	$P < 0.0001$
Schmorl's nodes	34 (64%)	6 (33%)	28 (80%)	$P = 0.0008$
Scheuermann-like kyphosis	23 (43%)	4 (22%)	19 (54%)	$P = 0.04$*
Platyspondylia	23 (43%)	5 (28%)	18 (51%)	$P = 0.13$

* Similar prevalence in adolescents and adults (4/9 *vs.* 19/35, $P = 0.72$).

like kyphosis was defined as a minimum of 5° of wedging in three consecutive vertebral bodies with associated endplate irregularities as suggested by Sorenson.[26] Platyspondylia and anterior scalloping were subjectively defined based on the appearance of the vertebral bodies.

Statistical comparisons of abnormal findings with age and back pain were performed by χ^2 analysis or Fischer's exact test (when necessitated by small cell numbers).

■ Results

The 53 patients ranged in age from 1 to 70 years (mean ± SD = 31 ± 19, median 30 years) with 23 males and 30 females (M:F = 1:1.3, $P = 0.50$). Eighteen patients were aged less than 18 years at the time of evaluation. One patient had undergone surgical correction of scoliosis, and another had undergone a lumbar laminectomy for nerve root compression.

Prevalence of radiographic abnormalities by age is shown in Table 2. Scoliosis was present in 18 patients (34%) with similar prevalence in pediatric and adult patients. One patient underwent surgical correction with Harrington rods at age 13 for an unknown preoperative curvature with postoperative 37° right thoracic and 28° left lumbar scoliosis at age 35. No other patients were treated with surgery or bracing. Mean primary curve in the 17 untreated patients was 14° (range, 10–26°). Eleven had a single thoracic curve (King Type 3) with mean 14° curvature (range, 10–26°). Three had a single lumbar curve of mean 11° (range, 10–12°). Two had double major curves (King Type 1) with thoracic curves of 11° and 15°. One patient displayed a complex pattern of a 12° midthoracic right curve, 12° lower thoracic left curve, and 22° lumbar right curve (Figure 2A and B). Excluding the one complex thoracolumbar pattern, four patients had primary left thoracic curves (mean 12°; range, 10–14°).

Endplate abnormalities (seen as irregular vertebral borders, sclerosis, disc space narrowing, and anterior cystic changes, Figure 2C; Figure 3, A and B, and Figure 4) were present in 39 patients (74%) with a large difference in prevalence between pediatric and adult patients (present in 6 of 18 children and 33 of 35 adults, $P < 0.0001$). The youngest patient with endplate abnormalities was 12 years of age.

Schmorl's nodes (Figures 3, A and B) were present in 34 patients (64%) with a bias toward adults (present in 6 of 18 children and 28 of 35 adults, $P = 0.0008$). The youngest patient with Schmorl's nodes was 12 years of age.

Twenty-three patients (43%) had focal thoracic kyphosis with associated vertebral wedging similar to that seen in Scheuermann's disease (Figure 2C; Figure 4). There was a statistically higher prevalence of this deformity in adult patients than in children. However, adolescents (the group most at risk for classic Scheuermann's disease) and adults had a similar prevalence (4/9 patients aged 12–17 compared with 19/35 adults, $P = 0.72$). No patients under age 12 had a Scheuermann-like deformity. Average three-segment deformity was 22.7 ± 4.9° (range, 15–36°). Fourteen of these patients displayed overall thoracic hyperkyphosis. No patients without a Scheuermann-like deformity had hyperkyphosis. One 45-year-old man without Scheuermann-like changes had reduced overall thoracic kyphosis (15° total).

Platyspondylia (Figure 2C) was present in 23 patients (43%) with similar prevalence in pediatric and adult patients. Seven patients (13%, average age, 33 years) had anterior scalloping of the lower thoracic and/or lumbar vertebral bodies (Figure 5). Six patients (11%, average age, 50 years) had Grade I spondylolisthesis of the L5–S1 junction. Four of these patients also had Scheuermann-like kyphotic deformities. Four patients had dramatic anterior bridging osteophytes (Figure 6), and less dramatic spurring was commonly observed.

Back pain was reported in 34 of 51 patients aged more than 5 years (67%) and was statistically associated with adult age ($P = 0.0002$), presence of vertebral endplate abnormalities ($P = 0.01$), and Schmorl's nodes ($P = 0.04$; Table 3). Back pain was not associated with sex, presence of scoliosis, Scheuermann-like kyphosis, or platyspondylia. Eighteen patients reported lumbar back pain only, 2 reported thoracic pain only, and 14 reported pain throughout both the thoracic and lumbar regions. In the 18 patients with lumbar pain, 5 had radiographic abnormalities confined to the lumbar region, 7 had both thoracic and lumbar abnormalities, and 6 had only thoracic abnormalities. The 2 patients who reported only thoracic pain had thoracic abnormalities only. Of the 14 patients reporting pain in both the thoracic and lumbar areas, 6 had only thoracic spinal abnormalities, 7 had both thoracic and lumbar spine abnormalities, and 1 had no radiographic abnormalities of the thoracolumbar spine. Six of 7 patients with anterior scalloping of the

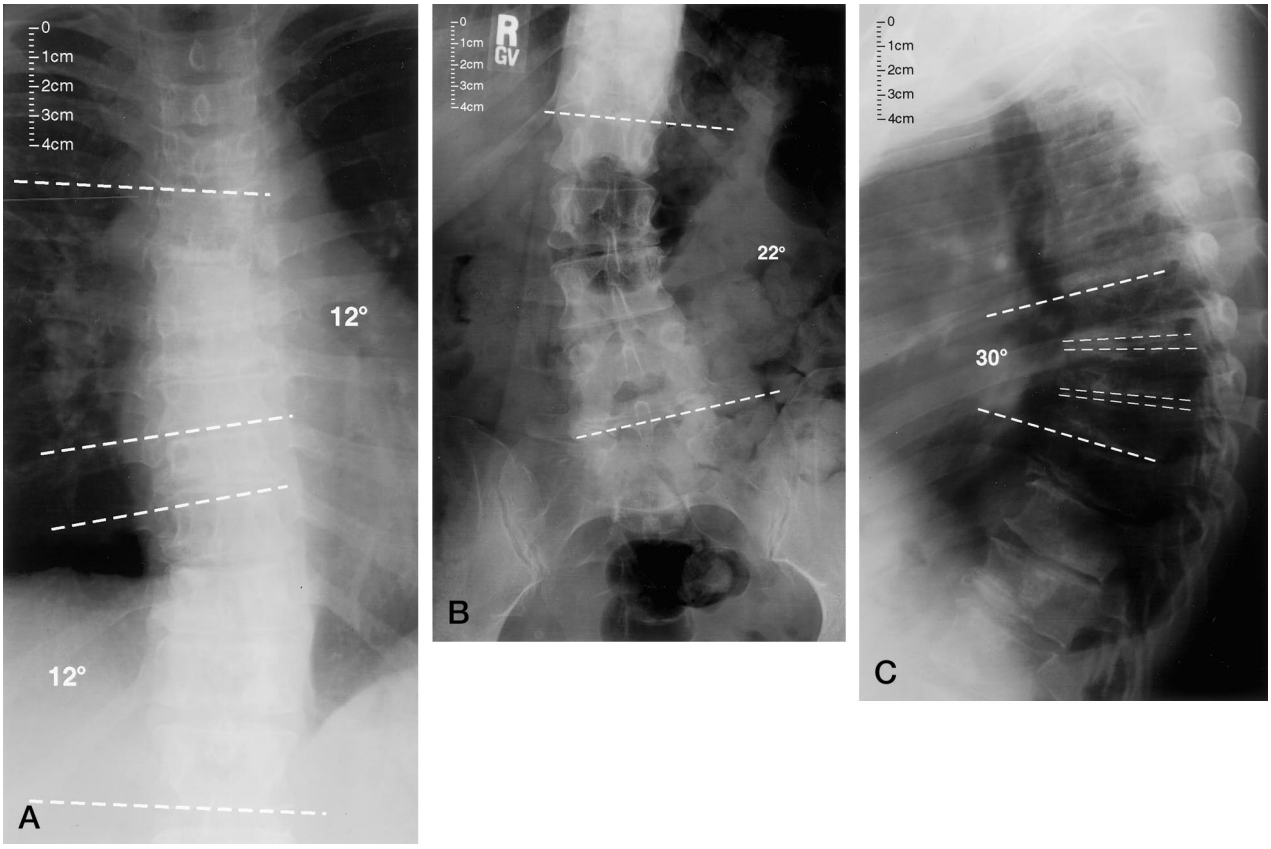

Figure 2. **A,** Anteroposterior thoracic and **B,** anteroposterior lumbar radiographs demonstrating double thoracic and single lumbar scoliotic curves in a 37-year-old woman; **C,** lateral thoracic radiograph in the same patient demonstrating extensive endplate sclerosis, Schmorl's nodes, platyspondylia, Scheuermann-like kyphosis, anterior spurring, and hyperkyphosis.

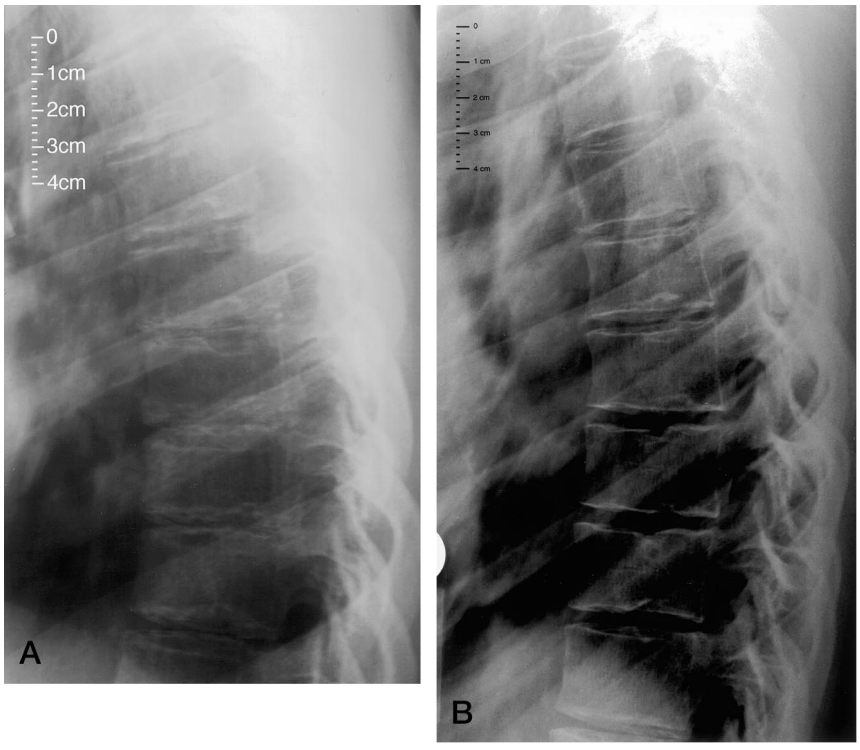

Figure 3. Extensive thoracic Schmorl's nodes in (**A**) a 16-year-old boy and (**B**) a 41-year-old woman.

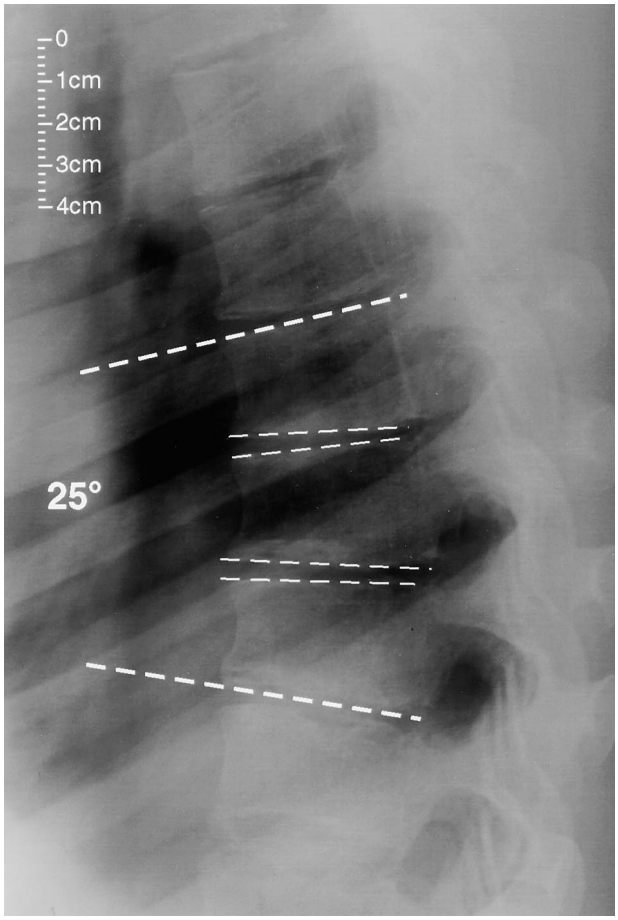

Figure 4. Scheuermann-like kyphosis (25°) in 17-year-old boy.

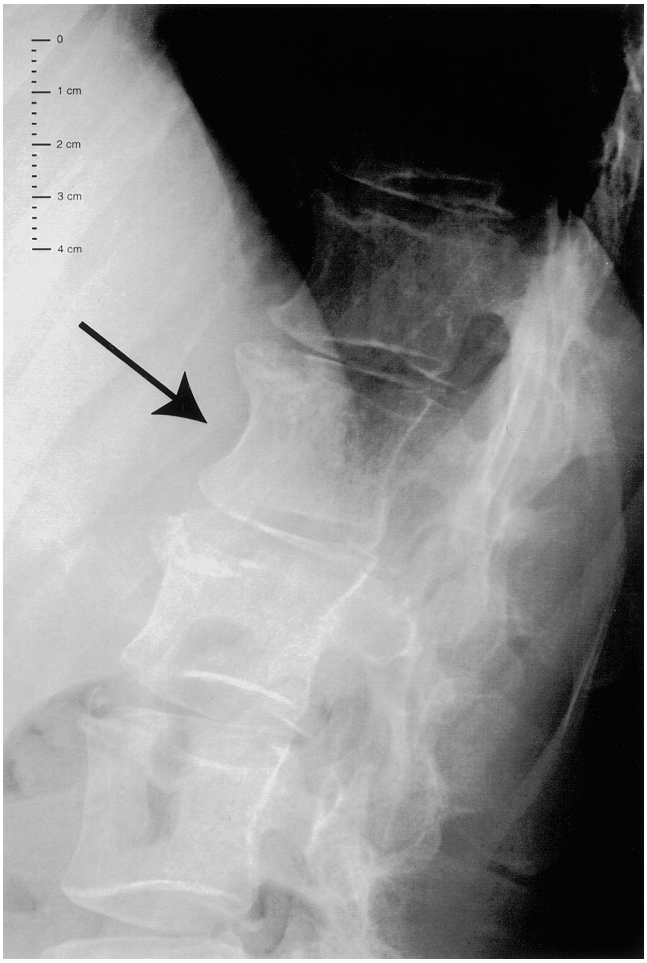

Figure 5. Large bridging osteophyte in lumbar spine in a 49-year-old man.

vertebral bodies and all 6 patients with spondylolisthesis reported back pain.

■ Discussion

This report provides the first analysis of thoracolumbar spinal abnormalities in a large series of patients with Stickler syndrome. The subjects all attended a comprehensive medical genetics clinic not focused on spinal deformities, which minimized selection bias caused by pain or dysfunction. The large number of families reduces the likelihood of bias toward a handful of mutations with severe phenotypes.

Approximately one third of patients had scoliosis, although only one underwent surgical correction, and to the authors' knowledge no others were treated with bracing. This indicates that scoliosis in Stickler syndrome is a common but usually self-limited condition with low probability of progressing to require operative intervention. Most thoracic curves found in patients with idiopathic scoliosis or skeletal dysplasias are convex to the right.[8] Four of 18 thoracic curves in this series had a primary left orientation, albeit with minor curves. The significance of this observation is unclear but is notably different from that observed in the Marfan syndrome, a common connective tissue disorder with frequent scoliosis.[28] There are no known neuromuscular disorders in Stickler syndrome to account for left curves, and the patterns observed were not the long C curves associated with neuromuscular conditions.[11]

The high frequencies of endplate abnormalities, Schmorl's nodes, and platyspondylia observed support the hypothesis that epiphyseal dysplasia frequently involves the spine in Stickler syndrome. These abnormalities were found most commonly in the thoracic and upper lumbar spine in concordance with previous case reports.[10,13,22]

Forty-three percent of patients displayed Scheuermann-like kyphosis in the thoracic spine, although to the authors' knowledge, none had had this condition previously diagnosed or treated. All 14 patients in this series with hyperkyphosis had Scheuermann-like deformities. The frequency was similar in adolescent and adult patients, which indicates that the deformities observed in adult patients are probably due to malformation of the vertebral bodies during growth rather than degenerative changes in adulthood. The absence of such deformities in any of the nine patients under age 12 implies this is unlikely to be a congenital deformity. It appears that focal thoracic kyphosis with vertebral wedging commonly develops in Stickler syndrome and often progresses to hyperkyphosis through adolescence and adulthood.

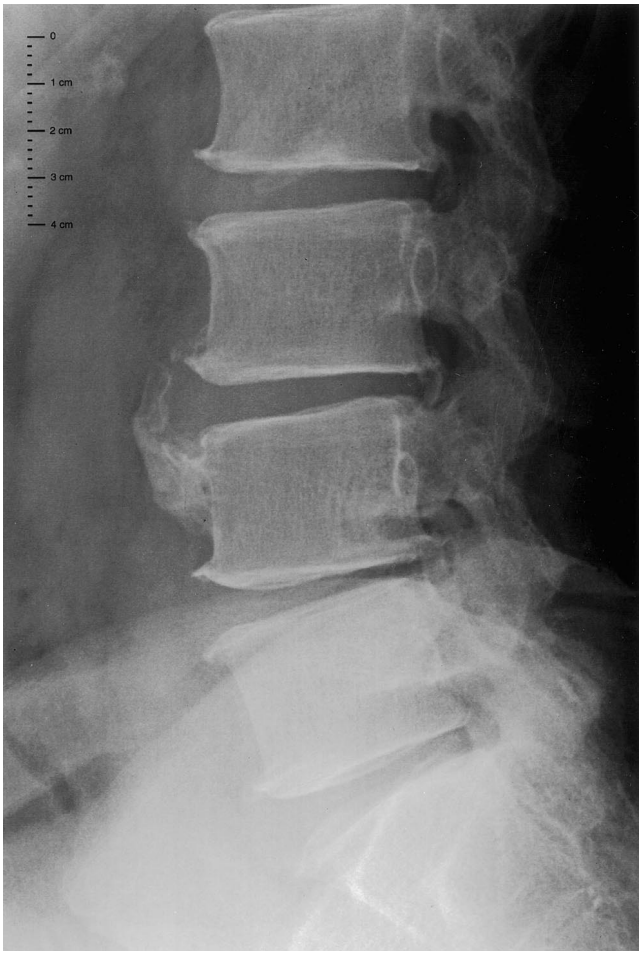

Figure 6. Anterior scalloping of lumbar vertebral bodies in a 36-year-old female.

A small number of patients had spondylolisthesis or anterior scalloping of the lower thoracic or lumbar vertebrae. Patients with anterior vertebral scalloping ranged in age from 7 to 57 years, implying that this is the result of developmental abnormalities in the spine rather than atypical degenerative changes. All patients with spondylolisthesis were adults with degenerative changes, raising the possibility that spondylolisthesis in Stickler syndrome results from progression of degenerative changes in the spine rather than a direct developmental abnormality. Although spondylolisthesis is often reported in conjunction with Scheuermann's disease,[34] the numbers in this study were too small to draw any correlation between spondylolisthesis and Scheuermann-like deformities.

Table 3. Association of Sex, Age, and Radiographic Abnormalities With Back Pain

	Percentage With Back Pain	Association With Back Pain
Sex	Male 12/22 (55%)	$P = 0.11$
	Female 22/29 (76%)	
Age	Pediatric 4/16 (25%)	$P = 0.0002$
	Adult 30/35 (86%)	
Scoliosis	12/18 (67%)	$P = 1.00$
Endplate abnormalities	30/39 (77%)	$P = 0.01$
Schmorl's nodes	26/34 (76%)	$P = 0.04$
Scheuermann kyphosis	15/23 (65%)	$P = 0.84$
Platyspondylia	16/24 (67%)	$P = 1.00$

Data on back pain missing on two patients less than 5 years old.

The pathophysiology of spinal abnormalities in Stickler syndrome has not been fully defined. Fibrillar collagen mutations associated with the syndrome (*COL2A1*, *COL11A1*, and *COL11A2*) presumably lead to malformation and weakening of intervertebral disks and vertebral endplates. The vertebral abnormalities, scolioses, and kyphotic deformities that were observed probably result from abnormal chondrification or endochondral ossification during development. This probably results in abnormal vertebral growth with exacerbation by premature degenerative changes in adulthood. The generalized joint hypermobility observed in Stickler syndrome probably accelerates this process. Although true longitudinal follow-up is necessary to draw direct conclusions, the authors believe the spinal manifestations observed in the adult patients are most likely the direct sequelae of fibrillar cartilage abnormalities and the resultant spondyloepiphyseal dysplasia.

Chronic back pain was reported by 85% of adult patients and was tightly correlated with age, vertebral endplate abnormalities, and Schmorl's nodes. Almost all patients reported lumbar pain, and many reported pain in both the thoracic and lumbar spine. One case of thoracic disc herniation leading to paraplegia has been reported,[9] several of the patients in this study were medically disabled by pain, and one had sustained a burst fracture of T12. This collection of findings highlights the clinical significance of spinal abnormalities in patients with Stickler syndrome. Further investigation is needed to determine the utility of prophylactic measures (*e.g.*, physical therapy, avoidance of high-impact activities) for modifying the natural history of back pain in Stickler syndrome.

Care should be taken when planning operative procedures in patients with Stickler syndrome. Unrecognized palatal abnormalities or midface hypoplasia can complicate airway management and contribute to upper or lower respiratory disease peri-operatively. Scheuermann-like kyphotic deformities, pectus excavatum or carinatum, and scoliosis are all common in Stickler syndrome, and all can impair pulmonary mechanics. Although the authors know of no formal evaluation of restrictive lung disease secondary to skeletal abnormalities in Stickler syndrome, careful attention to this may be appropriate until the natural history of spinal manifestations in this disorder is better characterized.

In summary, 46 of 53 patients with Stickler syndrome displayed some thoracolumbar spinal abnormality, and only 1 adult patient was free of abnormalities. Scoliosis was present in one third of patients but was generally mild. The high prevalence of back pain and its association with certain spinal abnormalities in this syndrome

indicates that patients are likely to come to orthopedic attention at an early age, often before the diagnosis of Stickler syndrome is made. A recent survey of patients with Stickler syndrome found that only a fraction of their orthopedic surgeons recognized their condition.[29] Although spinal deformities in Stickler syndrome are not known to necessitate treatment different from that for other spinal disorders, recognition of this syndrome is important to provide correct prognosis for spinal abnormalities, evaluation, and management of other systemic complications, and appropriate genetic counseling. Stickler syndrome should be considered in the differential diagnosis of young patients with spinal deformities, especially when accompanied by ocular, midface, audiologic, or other skeletal abnormalities.

■ Key Points

- Thoracolumbar spinal abnormalities are nearly uniformly observed in Stickler syndrome.
- Scoliosis was present in one third of patients but rarely required surgical or brace treatment.
- Radiographic abnormalities were correlated with back pain and age.

Acknowledgments

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