# The Hip in Stickler Syndrome

# \*†Peter S. Rose, M.D., †Nicholas U. Ahn, M.D., \*§Howard P. Levy, M.D., Ph.D., †‡Donna Magid, M.D., \*Joie Davis, M.S.N., C.P.N.P., \*Ruth M. Liberfarb, M.D., Ph.D., †Paul D. Sponseller, M.D., and \*Clair A. Francomano, M.D.

Study conducted at the Warren Grant Magnuson Clinical Center of the National Institutes of Health, Bethesda, Maryland, U.S.A.

**Summary:** Stickler syndrome is an autosomal dominant connective tissue disorder with a prevalence similar to that of Marfan syndrome. No previous study has examined hip pain or abnormalities in a large series of patients with Stickler syndrome. The purpose of this study was to describe hip abnormalities and their correlation with age and chronic hip pain in a cohort of 51 patients followed at the National Institutes of Health. Ten percent of patients had protrusio acetabuli, 21% coxa valga, and 34% of adults had hip osteoarthritis. Sixty-three percent of all patients and 79% of adults had chronic hip

Stickler et al. (39) first described a unique autosomal dominant syndrome of premature osteoarthritis, retinal degeneration, hearing loss, and orofacial abnormalities in 1965. The disorder (hereditary arthro-ophthalmopathy, or Stickler syndrome) is now known to be caused by mutations in the COL2A1, COL11A1, and COL11A2 procollagen genes of type 2 and 11 collagen (1,9,15,22, 34,44,47). Incidence is estimated at around 1/10,000, and Stickler syndrome may be the most common autosomal dominant connective tissue dysplasia in North America (11,17,27). Subsequent reports have expanded details of the ocular, skeletal, orofacial, and auditory features of the syndrome (11,19-21,27,28,30,31,33,40,45,48), and additional genetic heterogeneity is likely because linkage to the type 2 and 11 procollagen genes has been excluded in some families (22).

Type 2 collagen is a homotrimer of three COL2A1 gene products, whereas type 11 collagen is a heterotrimer containing one each of the COL2A1, COL11A1, and COL11A2 gene products (6). Both type 2 and 11 collagens are members of the fibrillar collagens, which are primarily expressed in cartilage, vitreous, and nucleus pulposus. Most patients with Stickler syndrome are

pain. In addition, 16% of adult patients had a history of femoral head failure during youth. Arthritic changes and adult age were associated with hip pain. In summary, hip abnormalities are commonly observed in Stickler syndrome. Young patients require careful evaluation of hip pain, and regular screening of children with Stickler syndrome may be indicated for early detection of hip complications. **Key Words:** Hereditary arthro-ophthalmopathy—Legg-Perthes disease—Osteoarthritis— Protrusio acetabuli—Slipped epiphysis—Stickler syndrome.

thought to have premature stop mutations in their COL2A1 gene, leading to the classic Stickler phenotype (type 1 Stickler syndrome) (25,36), and a COL2A1 mutation has been identified in the original family reported by Stickler (46). COL11A2 is not expressed in the vitreous, leading to a phenotype with systemic manifestations of Stickler syndrome but normal eye findings (non-ocular or type 2 Stickler syndrome) (24,35). Finally, a few families have been described with mutations in their COL11A1 gene (35). These patients display the classic phenotype, but subtle differences in the vitreoretinal abnormalities may be present. This variant is now referred to as type 3 Stickler syndrome (26).

Most patients are recognized in childhood if they present with cleft palate or severe ocular findings or have a positive family history. Approximately one fourth have an open cleft palate, and other patients have more subtle clefting (bifid uvula or submucous clefts) (19,21). Pierre-Robin sequence (the constellation of cleft palate, glossoptosis, and severe micrognathia, which can result in neonatal feeding problems and potentially lifethreatening respiratory obstruction) may be present. Other common facial features include malar hypoplasia, a flattening or widening of the nasal bridge, and micro/retrognathia. Figure 1 shows typical facial profiles in two patients over a range of ages. Widening of the nasal bridge and malar hypoplasia are most apparent when patients are young; micrognathia persists into adulthood.

High myopia generally develops in early childhood

Address correspondence and reprint requests to Dr. Peter Rose, Department of Orthopedic Surgery, The Mayo Clinic, 200 First St., SW, Rochester, MN 55905 (Rose.Peter@Mayo.edu).

From the \*National Human Genome Research Institute, National Institutes of Health, Bethesda; and the Departments of †Orthopaedic Surgery, ‡Radiology, and §Medicine, Johns Hopkins Hospital, Baltimore, Maryland, U.S.A.



FIG. 1. A-F: Facial photographs in two patients showing characteristic wide and flattened nasal bridge, malar hypoplasia, and micro/retrognathia.

and is associated with vitreous degeneration and a predisposition to retinal detachment and cataracts (excepting patients with type 2 or nonocular Stickler syndrome) (23,35,37). High-frequency sensorineural hearing loss advances with age (18,21). There are no known cognitive limitations in the syndrome.

Nearly all patients have evidence of spondyloepiphyseal dysplasia (37,38,45). One third of patients have scoliosis, and vertebral end-plate abnormalities, Scheuermann-like kyphotic deformities, platyspondyly, and spondylolisthesis are frequently present (17,30). Articular hypermobility can lead to joint instability with chronic effusions and progressive premature osteoarthritis, often beginning as early as the second decade (11, 18,28,29,39). This process frequently results in early disability, arthroplasty, or arthrodesis. Patients may have a marfanoid habitus and anterior chest wall deformities (pectus excavatum or carinatum), although height is generally normal (11,28,45). Anecdotal reports suggest that osteoporosis and ankle deformities may be common, but these have not been systematically evaluated. A recent series found that >85% of adults with Stickler syndrome reported chronic musculoskeletal pain, and one fourth were physically disabled from pain (31).

Specific hip manifestations of the syndrome include protrusio acetabuli, coxa valga, slipped epiphysis, Legg-Perthes-like disease, and chondrolysis (4,5,11,18,39). The femoral neck may be broad with a horizontal growth plate, and the femoral head and/or acetabulum may be misshapen (5,11). However, most descriptions come from case reports or small series. No previous study has examined the prevalence of hip pain and abnormalities in a large series of patients with Stickler syndrome.

#### METHODS

We reviewed radiographic and clinical data on 59 consecutive patients from 25 families with Stickler syndrome seen at the National Institutes of Health National Human Genome Research Institute medical genetics clinic during a 24-month period from 1997 to 1999. The average age was 29.2 years. There were 36 female patients and 23 male patients (chi square = 1.450, P =0.23). After written informed consent was obtained, patients were enrolled in a natural history and molecular etiology study approved by the National Human Genome Research Institute's Institutional Review Board (NIH protocol 97-HG-0089).

Skeletal surveys including pelvic and/or hip radiographs were prospectively obtained on all patients evaluated for Stickler syndrome. All patients were examined by one or more medical geneticists experienced in diagnosing Stickler syndrome and related connective tissue disorders (H.P.L., R.M.L., C.A.F.). Fifteen of these patients from four families have known COL2A1 mutations. No formal diagnostic criteria have been established for Stickler syndrome, although molecularly validated criteria are being developed (32). The working diagnostic criteria used at this center are presented in Table 1. Ophthalmologic findings and mutation analysis were used to differentiate families into type 1, 2, and 3 Stickler syndrome when possible.

Data on hip pain was taken from standardized pain inventories (the Wisconsin Brief Pain Inventory) (8), patient interviews, and musculoskeletal review of systems. Patients younger than 5 years of age were excluded from the pain analysis. Chronic hip pain was defined as documented reports of recurrent pain symptoms for >6 months.

Protrusio acetabuli was defined by projection of the acetabular line medial to the ilioischial line by >3 mm in male patients older than age 15, 6 mm in female patients older than age 15, 1 mm in boys younger than age 15, and 3 mm in girls younger than age 15, as suggested by previous studies (2,10). Neck-shaft angles were measured using the conventional technique on anteroposterior pelvis or hip radiographs. Normal values were considered to be  $120^{\circ}$  to  $140^{\circ}$  (13,42). Patients age 17 and older were considered skeletally mature.

Radiographic features of osteoarthritis were scored by an orthopaedic radiologist (D.M.) unaware of the presence of hip pain using the five-point grading standards described by Kellgren and Lawrence (14,16). Patients who had undergone total hip arthroplasty were considered to have had grade 4 (severe) changes.

Statistical comparisons were performed using chisquare analysis or the Fisher exact test (where appropriate due to small cell numbers).

### RESULTS

Data on hip pain were present for 51 patients older than age 5. Pelvic radiographs and/or hip films suitable for evaluation of the hip were prospectively available for 49 patients. Five patients (all younger than age 3) had no radiographs, four had incomplete skeletal surveys or missing films, and one (age 1 year) with a pelvic radiograph was excluded because of poor quality of the film due to positioning.

Two patients had a history of slipped capital femoral epiphysis in youth, three had a history of Legg-Perthes disease (Fig. 2), and one had a history of acute femoral head chondrolysis. One male patient with type 1 Stickler syndrome reported sudden severe hip pain while walking after a 2-month period of mild pain and limp at age 12. Slipped epiphysis was diagnosed, and he was treated with a spica cast for 6 weeks and crutches for 12 months. Further treatment reportedly included a Salter II pelvic osteotomy at age 16, but subsequent degenerative changes required total hip arthroplasty at age 29. A female patient with likely type 1 Stickler syndrome (severe eye changes precluded absolute differentiation from the type 3 phenotype) was diagnosed with slipped epiphysis at age 9 and treated with bilateral pinning after preslip was noted on the opposite side. Degenerative changes followed, and she underwent total hip arthroplasty of the presenting hip at age 26. Three additional patients had a history of Legg-Perthes disease (two male patients at age 5 and 10 and one female patient at age 9, two with type 1 disease and one with indeterminate eye findings). All were treated conservatively, although the two male patients (now age 18 and 37) are planning to undergo arthroplasty. Finally, one patient with type 2 (nonocular) Stickler syndrome presented with acute unilateral chondrolysis of the hip at age 14. She was initially diagnosed with possible inflammatory arthropathy, but all serologic markers and HLA-B27 testing were negative. She progressed to total hip arthroplasty at age 15. The original radiographs at the time of presentation could not be obtained for any of these patients to confirm the original diagnosis of slipped epiphysis, Legg-Perthes disease, or chondrolysis. All six patients now report hip pain. One additional patient underwent bilateral total hip arthroplasty at age 50 for severe degenerative changes, and several other patients are considering arthroplasty.

Protrusio acetabuli was present in seven hips in five patients (aged 13–55) out of 91 total hips with appropri-

Orofacial abnormalities (2 points maximum) (2 points)	Cleft palate (open cleft, submucous cleft, or bifid uvula)
(1 point)	Characteristic facies (malar hypoplasia, broad nasal bridge, and micrognathia)
Ocular abnormalities (2 points maximum)	
(2 points)	Characteristic vitreous degeneration or retinal detachment
Auditory abnormalities (2 points maximum)	
(2 points)	High-frequency sensorineural hearing loss
	Age <20: threshold $\geq$ 20 dB at 4–8 kHz
	Age 20–40: threshold $\geq$ 30 dB at 4–8 kHz
	Age >40: threshold $\geq$ 40 dB at 4–8 kHz
(1 point)	Hypermobile tympanic membranes
Skeletal abnormalities (2 points maximum)	
(1 point)	History of femoral head failure (typically 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	
(1 point)	First-degree affected relative in a pattern consistent with autosomal dominant inheritance

TABLE 1. Criteria used for diagnosis of Stickler syndrome

Diagnosis requires 5 points total and presence of cleft palate, ocular abnormalities, or high-frequency sensorineural hearing loss. Stature less than the fifth centile is suggestive of a skeletal dysplasia such as Kniest dysplasia or more severe spondyloepiphyseal dysplasia.



FIG. 2. Severely deformed hip in a 17-year-old boy with femoral head failure reported as Legg-Perthes disease at age 5.

ate radiographs (Fig. 3; analysis excludes five joints status post arthroplasty and two with severe femoral head deformity). Three of these patients had hip pain. Overall, 10% of patients evaluated (5/48) had protrusio in one or both hips.

The average neck-shaft angle of the femur (mean  $\pm$  standard deviation) was  $133.5^{\circ} \pm 8.2^{\circ}$ . Two patients had varus deformities in three hips (angle <120°) and 10 patients had valgus deformities in 13 hips (angle >140°; Fig. 4) in the 43 patients with films suitable for evaluation. Patients with abnormal neck-shaft angles were less likely to report hip pain, but this was association was not statistically significant (P = 0.08).

Osteoarthritis (defined as the presence of hip pain and grade 2, 3, or 4 radiographic degenerative changes using the Kellgren-Lawrence scoring system) was present in 19 hips in 13 patients (age 15–69; Figs. 5, 6). All patients with grade 2 or greater changes had hip pain. An additional 13 patients (age 13–70) had grade 1 radiographic changes in 18 hips. Ten of these patients reported hip pain. Hip pain was strongly associated with degenerative changes (Kellgren-Lawrence grade 2 or greater, P < 0.005).



FIG. 4. Coxa valga in a 10-year-old boy. Neck-shaft angles measure 150° and 156° (right/left).

Chronic hip pain was reported by 32 of 51 patients (63%; Fig. 7). Of 34 adult patients, 27 (79%) reported hip pain, and 7 (21%) were medically disabled primarily from musculoskeletal pain (2 other patients were disabled from blindness secondary to bilateral retinal detachment). Hip pain was not associated with gender (10 of 21 male patients with pain, 22 of 29 female patients with pain; P > 0.05) but was associated with adult age (5 of 17 minors with pain, 27 of 34 adults; P < 0.001). Pain was bilateral in almost all patients.

Thirty-one patients had known COL2A1 mutations or vitreoretinal changes in themselves or a family member indicative of type 1 Stickler syndrome. One patient had no ocular features of Stickler syndrome (nonocular or type 2 Stickler syndrome). Two patients had vitreoretinal changes indicative of type 3 Stickler syndrome. An additional 17 patients had vitreoretinal changes but were not differentiated into those typical of type 2 or type 3 Stickler syndrome. These patients generally had severe eye findings and frequently postsurgical changes that precluded accurate differentiation of ocular changes. There was no difference between patients with type 1 Stickler syndrome eye findings and those with indeter-



**FIG. 3.** Protrusio acetabuli in a 55-year-old woman. The left acetabular border is 7 mm medial to the ilioischial line.



FIG. 5. Bilateral osteoarthritic changes in a 49-year-old woman.



**FIG. 6.** Distribution of degenerative changes in the hip joint by age using the Kellgren-Lawrence grading scale.

minate eye findings with respect to chronic hip pain (P = 0.23) or osteoarthritis (P = 0.30).

#### DISCUSSION

This report provides the first analysis of radiographic abnormalities and hip pain in a large series of patients with Stickler syndrome. All patients in this study attended a comprehensive medical genetics clinic not directed toward musculoskeletal complaints, minimizing selection bias due to hip pain or dysfunction. The large number of families involved reduces the likelihood of bias toward a handful of mutations with severe phenotypes.

Although it may be the most common connective tissue disorder in North America and has prominent musculoskeletal manifestations, the orthopaedic literature contains scant reference to Stickler syndrome. Only six articles appear in the literature (4,5,7,17,38,43). Previous reports in other disciplines have described many of the radiographic features we observed, but none focused specifically on the hip or could quantify the prevalence of pain and other findings.

Chronic hip pain was common in our patients, with 79% of adults reporting pain and one fifth of adults medically disabled from musculoskeletal pain. These numbers may in fact underestimate hip pain in this population. In our experience, nearly all patients report knee



FIG. 7. Distribution of hip pain and physical disability by age.

pain, some of which may in fact be referred pain from the hip.

Using age- and sex-specific criteria, protrusio acetabuli was present in 10% of our patients. These patients ranged in age from 13 to 55 years, implying that these findings are more likely the result of developmental abnormalities than degenerative changes. This figure may underestimate the prevalence of protrusio in our patient population because the patients with total hip arthroplasty may also have had protrusio before their surgeries. Twenty-eight percent of patients had abnormal varus or valgus deformities of the femoral neck. Neither protrusio acetabuli nor abnormal neck-shaft angles were associated with hip pain. Long-term follow-up and biomechanical analysis will be required to define the natural history and potential significance of these findings in Stickler syndrome.

Premature degenerative changes have long been associated with Stickler syndrome but have never been quantified in the hip. One third of adult patients had osteoarthritis of the hip as defined by radiographic changes in conjunction with hip pain. The National Health and Nutrition Examination Survey found radiographic evidence of hip osteoarthritis in 3.1% of randomly surveyed individuals older than age 55 (41). Using a stricter definition than that study (requiring hip pain in conjunction with radiographic changes), we found hip osteoarthritis in 7 of 10 Stickler syndrome patients older than age 50 and 34% of all skeletally mature patients. In all likelihood, this premature joint failure results from a combination of articular cartilage defects, hypermobility, and the longterm consequences of epiphyseal dysplasia. Radiographic degenerative changes (Kellgren-Lawrence score  $\geq$ 2) were highly correlated with hip pain (*P* < 0.005).

Finally, 6 of 38 skeletally mature patients had a history of femoral head failure during youth. In two patients this is reported in their histories as a slipped capital femoral epiphysis, in three as Legg-Perthes disease, and in one as acute chondrolysis. All six patients now report hip pain, three have had total joint arthroplasty at age 15, 26, and 29, and two more, aged 18 and 37, are planning to undergo arthroplasty. The original radiographs from the time of presentation could not be obtained for analysis. Previous authors have reported cases of slipped capital femoral epiphysis, Legg-Perthes disease, and chondrolysis in patients with Stickler syndrome (5,18,39); Mc-Kusick (25) reported Stickler syndrome as a cause of "familial Legg-Perthes disease." Although the numbers in this study are limited, the incidence of slipped epiphvsis and Perthes disease in the general population is much lower than we have seen in this group (at most 7.7 and 1 per 10,000, respectively) (3,12).

Whether these findings represent distinct disease processes all associated with Stickler syndrome or are merely a single Stickler-related condition variously reported as slipped epiphysis, Perthes disease, and chondrolysis has not been determined. Regardless of the diagnostic terminology used, Stickler syndrome is clearly associated with femoral head failure presenting in childhood. The prevalence was 16% (6/38) among skeletally mature patients in this series. Deficiency or alteration of cartilage-associated fibrillar collagen is the presumptive cause of the congenital epiphyseal dysplasia in Stickler syndrome. This inherent weakness of the epiphyseal plate may predispose to slipped capital femoral epiphysis or Legg-Perthes-like disease. In addition, premature degenerative changes in the hip would be expected to increase the risk for premature femoral head failure.

As illustrated by our nonocular (type 2) Stickler syndrome patient, who was initially diagnosed with inflammatory arthropathy (but had subsequent negative serologies) to explain acute chondrolysis leading to arthroplasty at age 15, Stickler syndrome should be considered in the differential diagnosis of patients with otherwise unexplained hip abnormalities. Similarly, unexplained premature osteoarthritis of the hip should also prompt consideration of a diagnosis of Stickler syndrome. Finally, the high incidence of pediatric hip complications suggests that hip pain in children with Stickler syndrome requires careful evaluation. Until the natural history and etiology of hip abnormalities in the syndrome is better defined, periodic screening of young patients with Stickler syndrome for subtle signs of epiphyseal preslip, osteonecrosis, or other hip abnormalities may be appropriate.

Recognition of Stickler syndrome carries important medical and personal implications. The high frequency of musculoskeletal manifestations causes many patients to seek orthopaedic attention at an early age, often before Stickler syndrome is diagnosed. A recent survey of Stickler syndrome patients found that only a fraction of their orthopaedists recognized their condition (G. Stickler, personal communication, October 1999). Correct diagnosis of the syndrome is necessary to provide an accurate prognosis for spinal abnormalities, evaluation and management of other systemic manifestations, genetic counseling of affected families, and anticipation of potential perioperative complications when surgery is necessary (30). Stickler syndrome should be considered in the differential diagnosis of patients presenting with femoral head or acetabular abnormalities, spondyloepiphyseal dysplasia, or premature osteoarthritis, especially when accompanied by ocular, orofacial, auditory, or other skeletal abnormalities.

In summary, we analyzed hip pain and radiographic abnormalities obtained prospectively in a series of 51 patients with Stickler syndrome. Chronic hip pain was reported in 79% of adults, with 21% medically disabled from musculoskeletal pain. Protrusio acetabuli, coxa vara, and coxa valga were commonly seen but not clearly correlated with hip pain. Osteoarthritis was present in one third of skeletally mature patients. In addition, 16% of skeletally mature patients had a severe hip complication during their youth. Recognition of Stickler syndrome is important in children presenting with skeletal abnormalities. Young patients with Stickler syndrome require careful evaluation of hip pain, and regular screening of children with Stickler syndrome may be indicated for early detection of hip complications. Acknowledgments: The authors thank the patients and families in the NIH Stickler Syndrome Study for their participation in this study, with particular gratitude to the patients who donated photographs and gave permission for their use in this publication. This study was funded by a National Institutes of Health Intramural Research Grant (protocol 97-HG-0089).

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