Clinical features of hereditary progressive arthro-ophthalmopathy (Stickler syndrome): A survey

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Purpose: To define variations in the clinical manifestations of Stickler syndrome. **Methods:** A questionnaire was sent to 612 persons. **Results:** Of the 316 usable replies, 95% of persons had eye problems (retinal detachment occurred in 60% of patients, myopia in 90%, and blindness in 4%); 84% had problems with facial structures such as a flat face, small mandible, or cleft palate; 70%, hearing loss; and 90%, joint problems, primarily early joint pain from degenerative joint disease. Treatment included cryotherapy and laser therapy for retinal detachment, repair of cleft palate, use of hearing and mobility aids, and joint replacements. **Conclusions:** There are wide variations of symptoms and signs among affected persons, even within the same family. There are delays in diagnosis, lack of understanding among family members, denial about the risk of serious eye problems, and joint disease. **Genetics in Medicine, 2001;3(3):192–196.**

Key Words: cleft palate, hearing loss, myopia, premature degenerative joint disease, retinal detachment

Since the description of Stickler syndrome in 1965,¹ more than 100 articles have been published. Ten of these publications were review articles.^{2–14} The syndrome is a dominantly inherited disorder of collagen connective tissues, resulting in an abnormal vitreous of the eye, variable degrees of myopia, the risk of retinal detachment, cataract, and glaucoma. Hypermobility and early degenerative joint disease are common. Other manifestations may be cleft palate, orofacial abnormalities, and deafness. Recent progress at the molecular level has shown that Stickler syndrome can be due to mutations in the *COL2A1*, *COL11A1*, or *COL11A2* gene. Yet individual groups were able to examine only a limited number of affected individuals, and the natural history of the disease has not been studied. Although many people with Stickler syndrome belong to support groups in the United Kingdom (Stickler Syndrome Support Group), the United States (Stickler Involved People), The Netherlands, Canada, and Australia, there may be many more who have not been diagnosed or have been diagnosed and have chosen not to belong to a group. We surveyed group members to get a cross-sectional view of the clinical symptoms in the different age groups.

METHODS

A questionnaire (available on request) was designed with input from members of the support groups from the United Kingdom and the United States and with the help of ophthal-

mologists, otolaryngologists, and rheumatologists. It included questions about personal data, the age at diagnosis, and involvement of other family members. Major sections contained questions about eye involvement, facial features, hearing loss, skeletal involvement, the degree of handicap, and possible associations with other illnesses. Subsections dealt with treatments. In 1998, it was sent to 612 persons, all members of the support groups. They were returned to the offices of two major support groups where the names were removed and sent to the senior investigator for analysis. Normal data for height were used, as published by the National Center for Health Statistics. Chi-square tests were used to identify similarities or dissimilarities between the US and UK groups.

RESULTS

Of 330 questionnaires, 54% were returned from the United Kingdom, including 5 returns from The Netherlands and 23 from Australia, at first combined as the “UK group.” The rate of return from the United States was 50%, including 21 returns from Canada, combined as the “US group.” Fourteen returns were excluded from further analysis because they did not have a minimum of at least three of these manifestations: marked myopia, retinal detachment, cleft palate, Pierre Robin sequence, hypermobility of joints, early degenerative joint disease, and hearing loss. No significant differences were found between the replies from the United States and the United Kingdom.

In 91% of individuals, the diagnosis had been made or verified by health care professionals, most often geneticists or ophthalmologists. The remaining 9% had a positive family history and at least three of the manifestations of the syndrome as listed above. Of those diagnosed by a health professional as well as the 9% diagnosed on the basis of symptoms and signs, a total

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of 80% of the respondents had affected relatives. Among the 29 children who were diagnosed at birth, there were 24 who had affected relatives, 2 did not, and in 3 the question was not answered. There was no way to extract precise numbers from the answers to the questionnaire about how the knowledge of affected relatives influenced early diagnosis. This may well be true. It is also possible that the diagnosis in a newborn led to the diagnosis in other relatives. Among those diagnosed in the newborn period, there were 15 who had the Pierre Robin sequence.

For analysis, 152 children and adolescents younger than age 16 years and 164 adults remained. The oldest person was age 79 years. The male:female ratio was 0.9.

The heights were within normal limits. As a group, they were 0.12 SD above the mean for age and sex. To explore deviations from normal heights further, the number of individuals more than 3 SDs from the mean was determined. In the groups younger than 16 years, there were five individuals with heights >3 SD above the mean (3.1, 3.1, 3.4, 3.8, 3.8 SD) and five were more than 3 SD below the mean for age and sex (3.2, 3.5, 3.6, 3.6, 4.2 SD). One 16-year-old female who was 4.2 SD below the mean was quite handicapped, with skeletal involvement requiring her to use a wheelchair. She was wearing a back brace. Nothing was mentioned about the x-ray finding of her spine.

By calculating the body mass index (BMI), 21.2% of the US adult respondents were obese versus 13.8% of the patients in the United Kingdom (BMI > 30). The difference was not statistically significant (χ^2 test). In the latest SHANES, National Health and Nutrition Examination Survey of 1999, 27% of persons living in the United States between the ages of 20 and 74 years had a BMI of 30 or more. It is estimated that 13% of the adult population in the United Kingdom has a BMI of 30 or more. Of those who responded to the question about ethnic background, 304 persons were white, 2 were black, and 4 were mixed.

Half of the persons had some form of genetic counseling. Thirty-seven patients had been screened for mutations but results were known to only 31 persons (27 had *COL2A1* and 4 had *COL11A1*). No respondent had been identified as having mutation *COL11A2*. Although the number of defined mutations was small, differences between the clinical manifestations in the whole group and those with defined mutations could not be demonstrated. Specifically, of the four patients with *COL11A1*, two had the Pierre Robin sequence, two had hearing problems, three were myopic (−8.5, −12, and −2 diopters), but none had retinal detachments. One had glaucoma and cataracts. Two had hypermobility of joints and early onset of joint pain. In 29 patients, the diagnosis was made at birth. Sixty persons were older than age 30 years when the condition was diagnosed. The average age when the diagnosis was made was 21 years. The oldest person was age 72 years when the syndrome was identified.

Clinical manifestations

The symptoms of the disease were most carefully listed by the respondents. Disease severity and specific types of manifes-

tations varied widely between and within families. Ninety-five percent of the respondents had the typical manifestations of the syndromes affecting their eyes, 84% mouth and face, 70% hearing, and 90% joints.

Eye findings

Myopia was recorded in 90% of all individuals; 45% were able to state the degree of myopia in diopters, evidence of their careful reporting. In Table 1, the percentage of persons in various age groups who had detachment of the retina, cataracts, and glaucoma is shown. Retinal detachment occurred in 20% of children before the age of 10 years, but most frequently in persons between the ages of 10 and 30 years. The risk became smaller after age 40 years. No age-dependent trait was noted in the development of glaucoma. Eventually, about 60% of the whole group of affected individuals have had retinal detachments or cataracts (or both).

Cataracts without previous retinal detachment were recorded by 24% of the respondents (76% in persons who have had a retinal detachment). Glaucoma had been noted without retinal detachment in 7% of persons, but it was diagnosed in 34% after retinal detachment.

Eye treatment

Cryotherapy was used in children as young as age 1 year and in persons as old as 49 years and as often as four times. Laser treatments were done as early as age 1 year and as late as age 54 years (Table 2). Multiple treatments were often necessary (7 in 1 person).

To determine how many of the respondents were blind in one eye or both eyes, the responses to the question "Do you have vision in your left eye, right eye, or no vision?" were used and, in addition, participants were questioned about registration of impaired vision in the United Kingdom and in the United States (Table 3). The numbers would not be the same because the definition of registration as being blind, legal blindness, and self-assessment varied. Only 12 persons responded that they had lost vision in both eyes, and 50 had lost vision in one eye. Thirty-two persons knew that they suffered from Stickler syndrome when they had the first retinal detach-

Table 1
Eye problems present in various age groups

Age, y	Respondents, %		
	Retinal detachment	Cataracts	Glaucoma
0–9	8	8	7
10–19	26	35	10
20–29	61	39	19
30–39	62	62	20
40–49	57	61	4
50–59	65	76	35
≥60	60	60	27

Table 2
Treatment of retinal detachment and cataracts in survey respondents

Age, y	No.	Cryotherapy		Laser treatment		Vitreectomy	Cataract removal
		L	R	L	R		
0–9	87	7	18	8	13	9	10
10–19	77	13	20	21	24	8	16
20–29	35	13	8	15	11	5	13
30–39	39	3	9	9	9	8	8
40–49	46	2	5	8	10	2	18
50–59	16			1	1	4	7
60–79	15	1	4	1	1	1	8

Table 3
Status of vision in survey respondents

Age, y	Self-assessment		Registered			
	Vision in one eye, %	Blind, %	In UK	% ^a	In US	% ^a
0–9	1	0	As partially sighted	16	As legally blind	8
10–19	19	0	As blind	11	As legally blind without glasses	4
20–29	26	0				
30–39	31	5				
40–49	20	7				
50–59	37	6				
≥60	25	33				

^aCriteria differ in UK and US.

ment, and 37 knew that they had the symptoms of a retinal detachment. Forty-seven sought medical help immediately. At the time the questionnaire was completed by persons who knew that they had the syndrome, 83 persons stated that they would recognize the symptoms of retinal detachment now and 103 would seek medical help immediately.

Of the 62% who indicated whether they were advised to have first-degree relatives examined by an ophthalmologist, 78% answered affirmatively, but 13% were not told. The question did not apply to 9% of respondents.

Cleft palate and the Pierre Robin sequence

Forty-one percent of the respondents had a cleft palate. Of those, 75 had been diagnosed at birth with Pierre Robin sequence (Table 4). The presence of Pierre Robin sequence led to the diagnosis of Stickler syndrome in 11 newborns, in 22 infants during the first year of life, in 25 during the second year of life, and 17 later. The oldest were age 30 years when the connection between these syndromes was recognized. Individuals with Pierre Robin sequence all had problems breathing, feeding in early infancy only, but speech problems persisted in childhood. This finding is in contrast to children who had just

Table 4

Some characteristics of patients with Pierre Robin sequence ($n = 75$)

Characteristic	Patients, %
Hearing problem	85
Joint disease	86
Myopia	90
Retinal detachment	25
Glaucoma	12
Cataract	31

the cleft palate, with little or no micrognathia. Three of the children with Pierre Robin sequence required a tracheostomy for their breathing problem. Cleft palate repair was accomplished in most before age 2 years, but 18 had to wait longer, with 1 person in whom the repair was done at age 23 years. A total of five children needed a second operation for their cleft palate, and one person needed a third repair. One had five revisions. In an attempt to improve speech, 25 persons had a pharyngoplasty. Thirteen respondents had not indicated that they have had any repair.

Oral and facial manifestations

Half of the respondents believed that they had a flat midface (52%). Fourteen persons had nasal or midface grafts. Of all respondents, 47% reported having a small jaw, and 18 had a surgical procedure to improve this. Prominent eyes were reported by 35% and epicanthal folds were reported by 23%. Thirty-six percent were aware that they had a high-arched palate, and 16% had a bifid uvula. Fifty-five percent had malocclusion of teeth; of those, 35% had required orthodontic care.

Ear infections and hearing loss

Frequent ear infections were reported by 41% of all respondents. Of those with a cleft palate, 71% had frequent ear infections and the same percentage had fluid in their middle ear (glue ear). It was clear that the problems with ear infections, glue ear, and conductive hearing loss lessened with advancing age.

The problems with ear infections and serous otitis media were significantly more common in persons who had cleft palates even after they were repaired (71% vs. 31% and 71% vs. 15%, respectively, $P < 0.05$). Hearing loss was reported by almost half of the respondents. In children younger than age 16 years, 28% were thought to have conductive hearing loss, 31% sensorineural loss, and in 36% it was mixed. In adults, conductive hearing loss was reported in 3%; sensorineural, 29%; and mixed, 22%. The type of hearing loss was unknown in 29%. Only six persons considered themselves to be profoundly deaf. Hearing aids were used by one in five persons. Forty-five percent of individuals with combined hearing loss experienced tinnitus, as did 40% of those with sensorineural loss only. Tinnitus was also reported by 12% of persons with conductive hearing loss.

Skeletal manifestations

Genu valgum was noted primarily in children, with about one-fourth of the respondents mentioning it. None of them required surgical correction. This finding was also true for 17% who were thought to have scoliosis and persons with chest deformities (9% each having pectus excavatum and pectus carinatum). Three percent of patients with clubfeet had orthopedic corrections. Arachnodactyly was mentioned by three people. Hypermobility of joints was noted by 55% of respondents. This condition was more noticeable in 83% of children younger than age 10 years and decreased to 26% in persons older than 60 years. Enlarged joints were noted in more than half of the children younger than age 16 years and were still apparent to about a third of adults. Joint pain began early, particularly in the first decade of life (Table 5). By the time persons were older than age 40 years, more than 90% had joint pain. Heavy persons with body mass indices >25 did not report more pain than those with normal weight.

The pain was most often in the lower extremities, particularly in hips and knees. Most people (84%) recorded that the pain varied in intensity, but 16% had pain all the time. The pain appeared to be affected by weather in almost two-thirds of

Age at pain onset, y	Respondents, %	Replacements, no.
0–9	41	
10–19	29	Hips, 3
20–29	9	
30–39	11	Hips, 2; knee, 1
40–49	8	Hips, 5; knees, 2; shoulder, 1; finger, 1
50–59	2	Hips, 2
≥60		Hips, 7; knees, 2

persons, usually cold and wet, as well as changing weather. The time of day modulated the pain in 11%, often with more pain in the evening, and often after lying down. As expected, physical activity was associated with pain in 86% of persons; however, 45% of individuals also had pain with rest. Some women mentioned that the joint pain worsened during pregnancy.

Almost three-quarters of respondents (72%) stated that their daily mobility was affected. The joint problems altered the choice of sports or leisure activity, the distance to walk, and the time to stand in 70% to 80% of the respondents (Table 6). Balance was affected in 64% of persons, and 43% stated that their job or choice of career was affected. It was not clear whether obesity decreased activity or was the result of decreased activity. Because of severe joint involvement, 26 patients had joint replacements, primarily of hips; they were done as early as in the second decade of life (Table 5).

Joint stiffness was reported by 58%, occasional locking of joints by 34%. A small number of persons reported joint dislocations, primarily shoulder and fingers but also hips (7 persons) and knees (4 persons). One child was born with a congenital dislocation of the hip. The survey produced no reliable information about radiologic findings, but enlargement of joints (specifically the epiphysis), osteoarthritis, and vertebral changes were mentioned. In five children, a diagnosis of Legg-Calvé-Perthes disease had been made.

Mobility aids were used by one-fifth of the respondents. These were primarily canes; back, knee, and leg braces; correc-

Activity	Patients, %
Choice of sport or leisure activity	82
Distance to walk	79
Time to stand	74
Ability to climb stairs	70
Balance	64
Job or choice of career	43

tive shoes; inlays and arch supports; and wrist supports. Thirteen persons needed a wheelchair at least sometimes, 4 used a walker, and 4 used crutches. Seventy-eight percent of the persons answering the questionnaire were able to take care of themselves.

DISCUSSION

Study limitations

Although the persons surveyed were highly motivated and precise in filling out their questionnaires, there are some shortcomings. Only persons who had joined the support groups were contacted and of those, a little over 50% participated. It is possible that the more severely affected persons were more motivated to return the questionnaire. This may be counterbalanced by the possibility that those who were blind or most handicapped were unable to comply. Relatives who were added by some of the members may also have less severe manifestations. These are limitations of any such survey.

In this survey, it was impossible to assess the accuracy of the information given by the respondents. It was reassuring to see how carefully the patients answered questions regarding the degree of myopia and specific dates for the occurrence of complications or surgical interventions. The problems are those with any review of the past history, symptoms, and signs in clinical studies.

Yet, several important observations can be made from the summation of surveys completed by 316 individuals with Stickler syndrome. First, diagnosis is often delayed. This delay is attributable to underrecognition by health care providers, despite the fact that 80% of affected individuals had a positive family history. Delay of diagnosis is of special significance in this syndrome, because early diagnosis and intervention for retinal detachments can preserve vision. Greater education of members of families about the syndrome may also lead to earlier diagnosis in other family members. Second, the ear and eye manifestations tend to stabilize in adulthood, but the joint manifestations are progressive and impact significantly on activity level. Health care providers should recognize the likelihood of early degenerative joint disease. Third, many questions remain to be addressed such as the value of prophylactic

cryotherapy or laser therapy to prevent retinal detachment. Further phenotype-genotype work may clarify the role of specific collagen fibers.^{14,15} Variations in the vitreous phenotype can be caused by different substitutions in the X position of the type II collagen Gly-X-Y triple helix.¹⁶ Continued exploration of the relationship between Stickler syndrome and other type II collagen disorders (Marshall syndrome, Kniest dysplasia) is needed.

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