PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Pediatric Generalized Joint Hypermobility With and Without Musculoskeletal Complaints: A Localized or Systemic Disorder?

Raoul H. H. Engelbert, Ruud A. Bank, Ralph J. B. Sakkers, Paul J. M. Helders, Frits A. Beemer and Cuno S. P. M. Uiterwaal

Pediatrics 2003;111;e248
DOI: 10.1542/peds.111.3.e248

Pediatric Generalized Joint Hypermobility With and Without Musculoskeletal Complaints: A Localized or Systemic Disorder?

Raoul H. H. Engelbert, PhD, PT*; Ruud A. Bank, PhD‡§; Ralph J. B. Sakkers, MD, PhD‖; Paul J. M. Helders, PhD, PT*; Frits A. Beemer, MD, PhD¶; and Cuno S. P. M. Uiterwaal, MD, PhD#

ABSTRACT. *Objectives.* **Children with generalized hypermobility of the joints and musculoskeletal complaints frequently visit pediatric clinics, but many show no currently known collagen or other possibly related diseases. Whether the symptoms are confined to the musculoskeletal system is unknown. We assessed whether such children have detectable differences in laxity of connective tissue present in organ systems other than joints. We also assessed whether children with generalized joint hypermobility and musculoskeletal complaints have more profound systemic changes in connective tissue of various organ systems as compared with children with generalized joint hypermobility without musculoskeletal complaints.**

Methods. **Anthropometrics, range of joint motion, muscle strength, skin extensibility, blood pressure, quantitative ultrasound measurements of bone, and degradation products of collagen were studied in 15 prepubertal children with generalized joint hypermobility and musculoskeletal complaints and compared with a population-based reference group of 95 nonsymptomatic prepubertal children. Symptomatic hypermobile children were also compared with children of the population-based reference group who had asymptomatic hypermobility of the joints ($n = 16$).**

Results. **Children with symptomatic generalized joint hypermobility had significantly higher skin extensibility (5.6 mm/15 kPa, 95% confidence interval [CI]: 4.0–7.1), lower quantitative ultrasound measurements (speed of sound: −26.8 m/s; 95% CI: −41.1 to −12.6) in bone, and lower systolic and diastolic blood pressure (−8.0 mmHg, 95% CI: −13.3 to −2.8; and −6.0 mmHg, 95% CI: −10.0 to −2.2, respectively) as compared with the total reference group. Also, they had significantly lower excretion of urinary hydroxylysylpyridinoline cross-links (mean difference: −51.3 μmol/mmol; 95% CI: −92.2 to −10.4) as well as lysylpyridinoline cross-links (−18.7 μmol/mmol; 95% CI: −36.9 to −0.5). Age, gender, body weight, height, and particularly cross-links excretion did not explain group differences in clinical and bone characteristics. After adjustment for age, gender, body weight, and height, children with symptomatic generalized joint hypermobility ($n = 15$) had significantly higher total range of joint motion (117.8 degrees; 95% CI: 77.7–158.0), skin extensibility (3.5 mm/15 kPa; 95% CI: 1.6–5.3), lower quantitative ultrasound measurements in bone (speed of sound: −27.9 m/s; 95% CI: −48.4 to −7.5), borderline lower diastolic blood pressure (−4.9 mmHg; 95% CI: −10.7–0.9), and significantly higher degradation products in urine (hydroxyproline/creatinine: 21.2 μmol/mmol; 95% CI: 2.3–40.1) as compared with asymptomatic hypermobile children of the total reference group ($n = 16$). After adjustment for possible confounders, children with generalized joint hypermobility without musculoskeletal complaints had a significantly higher total range of joint motion and more profound skin extensibility, as compared with the reference group ($n = 79$).**

Conclusions. **Clinically manifested symptoms in otherwise healthy children with generalized joint hypermobility are accompanied by increases in the laxity of other body tissues. Thus, generalized joint hypermobility with musculoskeletal symptoms does not seem to be restricted to joint tissues. In symptomatic hypermobile children, a more systemic derangement was also present as compared with asymptomatic hypermobile children.** *Pediatrics* **2003;111:e248–e254. URL: http://www.pediatrics.org/cgi/content/full/111/3/e248; *joint hypermobility, collagen, skin extensibility, blood pressure, bone density, quantitative ultrasound measurements, functional ability.***

ABBREVIATIONS. SOS, speed of sound; Hyp, hydroxyproline; HP, hydroxylysylpyridinoline; LP, lysylpyridinoline; CI, confidence interval.

Generalized joint laxity is a clinically well-recognized feature of genetic syndromes, such as osteogenesis imperfecta, Ehlers-Danlos syndrome, and Marfan syndrome.[1,2] Such diseases are caused by various disorders of individual components of the connective tissue.[3–5] Besides laxity of joints and skin, pathologic phenomena in other organ systems are found such as in blood vessels, resulting in decreased blood pressure levels, and in bone, resulting in lower bone mass and abnormal bone structure.[6,7]

Children regularly visit pediatric clinics with musculoskeletal complaints resulting from generalized hypermobility of the joints. So far, no changes in collagen or in other extracellular matrix proteins have been reported. The prevalence of generalized joint hypermobility in children and adults varies be-

From the *Department of Pediatric Physical Therapy, Wilhelmina Children's Hospital, University Medical Center, Utrecht, the Netherlands; ‡Gaubius Laboratory, TNO Prevention and Health, Leiden, the Netherlands; §Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands; ‖Department of Pediatric Orthopedics, Wilhelmina Children's Hospital, University Medical Center, Utrecht, the Netherlands; ¶Department of Medical Genetics, Division of Biomedical Genetics, University Medical Center, Utrecht, the Netherlands; and #Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, the Netherlands.

Received for publication Jul 18, 2002; accepted Oct 14, 2002.

Reprint requests to (R.H.H.E.) Department of Pediatric Physical Therapy, Wilhelmina Children's Hospital, University Medical Center; Rm KB 02.056.0, Box 85090, 3508 AB Utrecht, the Netherlands. E-mail: r.engelbert@wkz.azu.nl

tween 10% and 25% and is related to age, gender, and race.[8–11] The prevalence of generalized joint hypermobility accompanied by musculoskeletal complaints in adults is approximately 3.3% among women and 0.6% among men.[12]

It might be that children with symptomatic generalized joint hypermobility are just a more extreme subset of the normal joint mobility distribution. However, it may also be that changes in connective tissue underlie these problems, albeit expectedly more subtle than in disorders in which, for example, collagen or fibrillin mutations have been found. If so, we hypothesized that connective tissue outside the joints are likely to be affected as well. We also hypothesized that in children with generalized joint hypermobility and musculoskeletal complaints, connective tissue outside the joints may be more affected than in children with generalized joint hypermobility without musculoskeletal complaints.

In this study, we assessed whether children with generalized joint hypermobility and musculoskeletal complaints had detectable differences with respect to organ systems other than joints and skin as compared with a population-based reference group. Furthermore, we assessed whether otherwise healthy children with generalized joint hypermobility and musculoskeletal complaints have changed connective tissue parameters. Finally, we assessed whether children with generalized joint hypermobility and musculoskeletal complaints have more profound systemic changes in connective tissue as compared with children with generalized joint hypermobility without musculoskeletal complaints.

METHODS

On the basis of adult criteria,[13] we classified children with generalized hypermobility of the joints to have musculoskeletal symptoms in cases of arthralgia in more than 2 joints for a period exceeding 12 weeks, exercise-induced pain and intolerance, without the presence of signs of any rheumatic, neurologic, skeletal, or metabolic disease. Included in this study were 15 consecutive prepubertal white children with generalized joint hypermobility and musculoskeletal complaints as defined. All were examined clinically by a senior clinical geneticist (F.A.B.). There were no signs or symptoms indicating (known) collagen disorders or other syndromes involving joint laxity.

As a reference, the Montessori school (n = 303) and Jenaplan-school Het Spoor (n = 311), 2 primary schools in the city of Zeist in the center of the Netherlands for children ages 4 years (kindergarten) to 12 years (8th grade) were used. All 173 healthy young pupils between 8 and 10 years from both schools were invited to participate. Of these, 117 (response rate: 68%) agreed and were examined during special sessions at school during a 3-week period in November 2000. On the basis of a parental questionnaire, children with past or present signs of any rheumatic, neurologic, skeletal, metabolic, or collagen disease were excluded (n = 2). Because ethnic background is believed to determine joint mobility, all nonwhite children were excluded, leaving 95 white children available for analysis. In this reference group, all children with generalized joint hypermobility without musculoskeletal complaints were identified and also served as a reference group for the study population. The first author (R.H.H.E.) performed all measurements. He was not blinded for the children with symptomatic generalized joint hypermobility, but he was blinded for the total reference group with and without asymptomatic generalized joint hypermobility.

Body height and weight were measured in a standardized manner without shoes and heavy clothing, to the nearest centimeter and 100 g, respectively.[14] Range of joint motion was measured to assess ligamentous laxity, as a possible result of the amount of collagen and cross-links in the periarticular structures.[15] The active range of joint motion of the shoulder (anteflexion), elbow (flexion and extension), wrist (palmar and dorsal extension), hip (flexion and extension), knee (flexion and extension), and ankle (plantar and dorsal extension) was measured bilaterally to the nearest 5 degrees with a standard 2-legged 360-degree goniometer, using the "anatomic landmark" method.[16] Total range of joint motion was a summation of all measurements.

The extent of generalized hypermobility of the joints was quantified using the hypermobility score of Bulbena et al.[17] The presence of hypermobility was scored in 9 joints (thumb, little finger, elbow, shoulder, hip, knee, patella, ankle, and metatarsophalangeal I joint), and the presence of ecchymoses was recorded (maximum score: 10 points). Generalized hypermobility of the joints was considered present when the score was at least 5 in girls and at least 4 in boys.

Muscle strength of the proximal and distal muscles in lower and upper extremities was measured with a hand-held myometer to provide insight in the musculoskeletal complaints, to assess differences between the symptomatic hypermobile children and the reference population, and to explain differences in active range of joint motion.[18] Measurements were consecutively performed 3 times, and the highest value was registered. In the upper extremity, shoulder abductors and grip strength were measured; in the lower extremity, hip flexors and dorsal extensors of the foot were measured. Total muscle strength was analyzed as a summation of all measurements.

With the use of a vacuum tissue compliance meter, skin extensibility was measured bilaterally at the ventral part of the forearm and at the medial part of the upper leg. The amount of skin displacement was indicated in millimeters using a negative pressure of 15 kPa. The reliability of this instrument was previously shown to be high.[19] Total skin extensibility was analyzed as a summation of all measurements.

Blood pressure was measured, providing information on stiffness of the arterial wall and at least partly relating to the status of arterial wall connective tissue.[20,21] Blood pressure was measured after 5 minutes of rest at both the start and the end of the examination using the noninvasive automated Omron R3 (CEMEX Medical Technics, Nieuwegein, The Netherlands), which seemed to be a reliable and accurate device.[22] The mean of 2 measurements was used for analysis.

Quantitative ultrasound measurement was performed as a noninvasive method of bone quantity assessment and providing information of bone structure.[23–25] Measurements of the right os calcis were performed with a Sahara ultrasound device (Hologic QDR 4500; Hologic Inc, Waltham, MA) measuring broadband ultrasound attenuation (dB/MHz) and speed of sound (SOS; m/s) as indicators of bone quantity and bone stiffness, respectively. Acoustic phantoms provided by the manufacturer were scanned daily and showed no drift over the time period of the study.

Degradation products of collagen (hydroxyproline [Hyp]; cross-links) were measured in urine specimens. Spot samples were hydrolyzed overnight in 6 M HCl in Teflon-sealed glass tubes. Hyp and cross-link analysis (hydroxylysylpyridinoline [HP] and lysylpyridinoline [LP]) was conducted as described previously.[26,27]

A parental questionnaire provided information concerning the child's health status, presence of familial hypermobility, hours of sports activities, and the presence of exercise-induced pain in or complaints about the musculoskeletal system. The Medical Ethics Committee of the Wilhelmina Children's Hospital (University Medical Center Utrecht) approved this study, and informed consent was obtained from all parents.

Statistical Analysis

Central estimators of all relevant variables were calculated as means (standard error of the mean) or medians (minimum, maximum) when appropriate. The data were analyzed with linear regression using a group indicator as independent variable. Results are presented as linear regression coefficients of the group indicator representing mean group differences with their corresponding 95% confidence intervals (CIs). The same models were used to adjust for possible confounding factors. Statistical significance was considered reached when 95% CIs did not include the null value. Differences in Bulbena score were analyzed nonparametrically (Mann-Whitney U test).

RESULTS

Table 1 shows clinical characteristics, quantitative ultrasound measurements, and collagen degradation products. There were small group differences in age, gender distribution, and weight.

The median Bulbena score was 6 (25th percentile–75th percentile: 6–7) in children with symptomatic generalized joint hypermobility, 5 (25th percentile–75th percentile: 4–5) in the asymptomatic group with generalized joint hypermobility ($P < .001$), and 1 (25th percentile–75th percentile: 0–1) in the reference group ($P < .001$). Although in symptomatic hypermobile children arthralgia and exercise-induced pain and intolerance were present, no significant difference in time of sport activities was found compared with the reference group (median hours of sport activities in symptomatic hypermobility: 1 (25th percentile–75th percentile: 1–2); reference group: 2 (25th percentile–75th percentile: 1–3; $P = .12$). Symptomatic hypermobile children more often reported a family history of joint hypermobility than did the asymptomatic hypermobile children and the total reference group (47.0%, 13.3%, and 15.2%, respectively).

Table 2 shows that in children with symptomatic generalized joint hypermobility, a more profound skin extensibility, lower quantitative ultrasound measurements (SOS), systolic and diastolic blood pressures, and HP and LP cross-links were significantly different from the total reference group ($n = 95$). All group differences were additionally adjusted for age, gender, body height, and weight, as these are determinants for blood pressure, joint mobility, skin extensibility, and quantitative ultrasound measurements.[23,24,28,29] As shown in the fourth column of Table 2, this adjustment had only a marginal influence on the results. We further assessed whether findings concerning urinary excretion of collagen degradation products might explain group differences in other clinical characteristics. However, the last column of Table 2 shows that none of the differences in clinical characteristics or bone ultrasound measurements was explained by adjustment for the differences in urinary cross-link excretion (HP).

Children with symptomatic generalized joint hypermobility had significantly higher total range of joint motion, more profound skin extensibility, significantly lower quantitative ultrasound measurements (SOS), and lower diastolic blood pressure as compared with the asymptomatic hypermobile group ($n = 16$; Table 3). Systolic blood pressure and LP cross-links seemed lower, although these differences were not statistically significant. All group differences were also adjusted for age, gender, body height, and weight. Children with symptomatic generalized joint hypermobility had significantly higher total range of joint motion, more profound skin extensibility, significantly lower quantitative ultrasound measurements (SOS), and significantly higher Hyp excretion in urine as compared with the asymptomatic hypermobile group ($n = 16$; Table 3, fourth column). Diastolic blood pressure and quantitative ultrasound measurements (broadband ultrasound attenuation) seemed lower, although these differences were not statistically significant.

Children with generalized joint hypermobility without musculoskeletal complaints had significantly higher total range of joint motion, more profound skin extensibility, and lower total muscle strength as compared with the reference group ($n = 79$; Table 4). All group differences were also adjusted for age, gender, body weight, and height. After adjustment, children with asymptomatic generalized joint hypermobility had significantly higher total range of joint motion and more profound skin extensibility (Table 4, fourth column).

TABLE 1. General Characteristics

	Generalized Joint Hypermobility With Musculoskeletal Complaints ($n = 15$)	Generalized Joint Hypermobility Without Musculoskeletal Complaints ($n = 16$)	Reference Group ($n = 79$)
Clinical characteristics			
Age (y)	8.1 (2.5)	8.9 (0.7)	9.3 (0.7)
Gender (% girls)	60	75	53
Body height (m)	1.34 (0.2)	1.36 (0.07)	1.39 (0.1)
Body weight (kg)	30.3 (10.4)	29.2 (4.5)	32.5 (6.0)
Quetelet index (kg/m^2)	16.4 (2.0)	16.0 (1.7)	16.5 (1.6)
Bulbena score (P50; P25-75)	6 (6-7)	5 (4-5)	0 (0-1)
Total range of joint motion (degrees)	1743.2 (46.0)	1629.4 (44.3)	1542.5 (48.3)
Systolic blood pressure (mm Hg)	100.2 (8.7)	106.7 (10.5)	110.8 (9.4)
Diastolic blood pressure (mm Hg)	64.3 (6.3)	70.1 (6.7)	71.9 (6.8)
Pulse pressure (mm Hg)	35.8 (7.2)	36.6 (6.6)	38.9 (7.0)
Total muscle strength (N)	782.2 (224.2)	783.2 (120.7)	858.4 (127.7)
Total skin extensibility (mm)	41.5 (1.2)	37.7 (2.5)	35.5 (2.8)
Quantitative bone ultrasound measurements			
BUA (dB/MHz)	50.4 (10.3)	57.9 (13.9)	57.6 (14.4)
SOS (m/s)	1544.6 (15.1)	1575.6 (27.7)	1569.8 (23.2)
Collagen biochemistry			
Hyp/creatinine (μmol/mmol)	123.1 (33.8)	106.1 (25.1)	113.3 (26.7)
HP/creatinine (μmol/mmol)	214.5 (69.0)	250.3 (76.0)	250.9 (69.2)
LP/creatinine (μmol/mmol)	59.1 (21.5)	75.2 (27.3)	74.8 (32.2)
Ratio HP/LP	3.7 (0.5)	3.5 (0.6)	3.6 (0.8)

Values are means standard deviation, unless otherwise indicated.
P25 indicates 25th percentile; P75, 75th percentile; BUA, broadband ultrasound attenuation.

TABLE 2. Clinical Characteristics, Bone Ultrasound Measurements, and Collagen Biochemistry in Children With Generalized Joint Hypermobility and Musculoskeletal Complaints and the Total Reference Group

	Generalized Joint Hypermobility With Musculoskeletal Complaints (n = 15)	Total Reference Group (n = 95)	Mean Difference (95% CI)	Mean Adjusted Difference (95% CI)*	Mean Adjusted Difference (95% CI)†
Clinical characteristics					
Age (y)	8.1 (0.6)	9.2 (0.1)	−1.2 (−1.8, −0.5)		
Body height (m)	1.3 (0.04)	1.4 (0.01)	−0.5 (−0.1, 0.01)		
Body weight (kg)	30.3 (2.7)	31.9 (0.6)	−1.6 (−5.3, 2.0)		
Quetelet index (kg/m²)	16.4 (0.5)	16.5 (0.2)	−0.1 (−1.0, 0.8)		
Total range of joint motion (degrees)	1743.2 (12.3)	1557.2 (5.9)	**186.1 (154.1, 218.0)**	**177.0 (145.1, 208.9)**	**181.6 (147.7, 215.6)**
Systolic blood pressure (mm Hg)	100.2 (2.4)	110.1 (1.0)	**−9.9 (−15.5, −4.3)**	**−8.0 (−13.3, −2.8)**	**−8.0 (−13.4, −2.6)**
Diastolic blood pressure (mm Hg)	64.3 (1.7)	71.6 (0.7)	**−7.2 (−11.2, −3.3)**	**−6.0 (−10.0, −2.2)**	**−5.5 (−9.5, −1.4)**
Pulse pressure (mm Hg)	35.9 (2.0)	38.6 (0.7)	−2.7 (−6.8, 1.4)	−1.9 (−6.0, 2.1)	−2.5 (−6.8, 1.7)
Total muscle strength (N)	782.2 (62.2)	846.8 (13.5)	−64.7 (−149.0, 19.7)	3.2 (−50.8, 57.3)	10.1 (−44.9, 65.1)
Total skin extensibility (mm)	41.5 (0.3)	35.9 (0.3)	**5.6 (4.0, 7.2)**	**5.6 (4.0, 7.1)**	**5.5 (3.9, 7.1)**
Quantitative bone ultrasound measurements					
BUA (dB/MHz)	50.5 (2.7)	57.7 (1.5)	−7.2 (−15.3, 0.9)	−7.2 (−15.4, 1.4)	−7.3 (−16.1, 1.4)
SOS (m/s)	1544.6 (5.1)	1570.7 (2.5)	**−26.1 (−39.8, −12.4)**	**−26.8 (−41.1, −12.6)**	**−26.4 (−40.9, −11.8)**
Collagen biochemistry					
Hyp/creatinine (μmol/mmol)	123.1 (8.7)	112.1 (2.7)	11.1 (−4.1, 26.3)	3.9 (−11.8, 19.5)	
HP/creatinine (μmol/mmol)	214.5 (17.5)	250.8 (7.2)	**−42.7 (−82.2, −3.3)**	**−51.3 (−92.2, −10.4)**	
LP/creatinine (μmol/mmol)	59.1 (5.9)	74.9 (3.2)	−16.7 (−33.9, 0.5)	**−18.7 (−36.9,−0.5)**	
Ratio HP/LP	3.7 (0.2)	3.6 (0.1)	−0.09 (−0.3, 0.5)	0.1 (−0.3, 0.6)	

Values are means (standard error of the mean), unless otherwise indicated. Statistically significant associations were considered reached when 95% CIs did not include the null value and are given in **boldface**.

* Adjustment for age, gender, body height, and body weight.

† Adjustment for age, gender, body height and weight, and HP/creatinine.

TABLE 3. Clinical Characteristics, Bone Ultrasound Measurements, and Collagen Biochemistry in Children With Generalized Joint Hypermobility With and Without Musculoskeletal Complaints

	Generalized Joint Hypermobility With Musculoskeletal Complaints (n = 15)	Generalized Joint Hypermobility Without Musculoskeletal Complaints (n = 16)	Mean Difference (95% CI)	Mean Adjusted Difference (95% CI)*
Clinical characteristics				
Age (y)	8.1 (0.6)	8.9 (0.2)	−0.8 (−2.1, 0.4)	
Body height (cm)	1.30 (0.04)	1.36 (0.02)	−0.02 (−0.1, 0.1)	
Body weight (kg)	30.3 (2.7)	29.2 (1.1)	1.2 (−4.7, 7.0)	
Quetelet index (kg/m^2)	16.4 (0.5)	15.6 (0.3)	0.8 (−0.4, 2.0)	
Total range of joint motion (degrees)	1743.2 (12.3)	1629.4 (11.1)	**114.8, (80.9, 148.8)**	**117.8 (77.7, 158.0)**
Systolic blood pressure (mm Hg)	100.2 (2.4)	106.7 (2.6)	−6.5 (−13.9,1.0) (P = .09)	−6.0 (−13.6, 1.6)
Diastolic blood pressure (mm Hg)	64.3 (1.7)	70.1 (1.7)	**−5.7 (−10.7, −0.7)**	−4.9 (−10.7, 0.9) (P = .09)
Pulse pressure (mm Hg)	35.9 (2.0)	36.6 (1.6)	−0.8 (−6.0, 4.5)	−1.0 (−5.9, 3.8)
Total muscle strength (N)	782.2 (62.2)	783.2 (32.3)	−1.0 (−142.3, 140.2)	1.5 (−81.5, 84.5)
Total skin extensibility (mm)	41.5 (0.3)	37.7 (0.6)	**3.8 (2.2, 5.3)**	**3.5 (1.6, 5.3)**
Quantitative bone ultrasound measurements				
BUA (dB/MHz)	50.4 (2.7)	57.9 (3.6)	−7.4 (−16.9, 2.1)	−9.9 (−20.4, 0.5) (P = .06)
SOS (m/s)	1544.6 (5.1)	1575.6 (7.1)	**−31.0 (−49.5, −12.5)**	**−27.9 (−48.4, −7.5)**
Collagen biochemistry				
Hyp/creatinine (μmol/mmol)	123.1 (8.7)	106.1 (6.3)	17.0 (−4.8, 38.8)	**21.2 (2.3, 40.1)**
HP/creatinine (μmol/mmol)	214.50 (17.5)	250.3 (19.0)	−35.8 (89.9, 18.3)	−35.4 (−101.1, 30.2)
LP/creatinine (μmol/mmol)	59.1 (5.9)	75.3 (6.8)	−16.2 (−34.7, 2.4) (P = .08)	−16.8 (−39.0, 5.4)
Ratio HP/LP	3.7 (0.2)	3.5 (0.2)	0.2 (−0.2, 0.7)	0.3 (−0.2, 0.8)

Values are means (standard error of the mean), unless otherwise indicated.
* Adjustment for age, gender, body height, and body weight. Statistically significant associations were considered reached when 95% CIs did not include the null value and are given in **boldface**.

DISCUSSION

We found that otherwise healthy children with symptomatic joint hypermobility as their only complaint show changes in various organ systems, including the locomotor system. Higher joint mobility and skin extensibility and lower blood pressure, bone density, and urinary cross-link excretion in children with symptomatic generalized hypermobility may be attributed to constitutional interindividual differences in connective tissues. We also found that otherwise healthy children with symptomatic joint hypermobility as their only complaint show significant changes in various organ systems as compared with asymptomatic hypermobile children.

Our study included a limited number of children with symptomatic and asymptomatic joint hypermobility and may therefore be underpowered for some of the associations studied. However, differences between the groups are plausible and may reflect strong associations.

In principle, the cross-sectional design does allow for the inference that systemic changes may merely reflect immobility driven by complaints, as observed in adults with collagen disorders.[7] However, some of our findings may point toward another explanation. At entry into our study, symptomatic hypermobile children were not less active than their nonsymptomatic peers. Moreover, whereas immobility may have strong effects on bone and muscle,[30] it does not easily explain some other group differences, such as blood pressure, joint hypermobility, and skin hyperextensibility. We consider highly unlikely the possibility that among the healthy children the nonresponse to our invitation to participate was based on a specific relation between mobility and other measured characteristics, thus inducing selection bias. Although we did adjust for variables that might be confounders given current knowledge, there may be residual confounding or confounding by factors that we do not know yet. Besides the amount of activity, vitamin D and osteocalcin influence bone mineral density. Because the Medical Ethics Committee of our hospital did not agree with collecting blood samples, these aspects could not be studied.

To our knowledge, systemic features in conjunction with symptomatic hypermobility have not been reported before. Only in adults with established collagen disorders, such as Ehlers-Danlos syndrome, have systemic characteristics been described.[6,7] Research in healthy subjects showing associations between connective tissue components of different organ systems is scant. In adults, the presence of spontaneous cervical artery dissections was associated with ultrastructural abnormalities in the skin, such as those found in systemic collagen disorders such as Ehlers-Danlos–type syndromes.[31]

In children and adults, pain and distress of visceral origin can result from laxity of connective tissue providing support for the abdominal, thoracic, or pelvic viscera leading to hernia, uterine and/or rectal prolapse, mitral valve prolapse, or spontaneous pneumothorax.[32] Therefore, it is an important clinical implication also to look for abnormal connective tissue in nonjoint organ systems.

TABLE 4. Clinical Characteristics, Bone Ultrasound Measurements, and Collagen Biochemistry in Children With Generalized Joint Hypermobility Without Musculoskeletal Complaints and Reference Group

	Generalized Joint Hypermobility Without Musculoskeletal Complaints (n = 16)	Reference Group (n = 79)	Mean Difference (95% CI)	Mean Adjusted Difference (95% CI)*
Clinical characteristics				
Age (y)	8.9 (0.2)	9.3 (0.7)	**−0.4 (−0.8, −0.06)**	
Body height (cm)	1.36 (0.02)	1.39 (0.1)	−0.03 (−0.07, 0.02)	
Body weight (kg)	29.2 (1.1)	32.5 (6.0)	**−3.4 (−6.5, −0.2)**	
Quetelet index (kg/m^2)	15.6 (0.3)	16.5 (1.6)	**−1.0 (−1.9, −0.2)**	
Total range of joint motion (degrees)	1629.4 (11.1)	1542.5 (48.3)	**86.8 (60.9, 112.8)**	**72.5 (45.1, 99.8)**
Systolic blood pressure (mm Hg)	106.7 (2.6)	110.8 (9.4)	−4.1 (−9.3, 1.1)	−1.9 (−7.0, 3.3)
Diastolic blood pressure (mm Hg)	70.1 (1.7)	71.9 (6.8)	−1.8 (−5.5, 1.9)	−0.6 (−4.3, .1)
Pulse pressure (mm Hg)	36.6 (1.6)	38.9 (7.0)	−2.3 (−6.1, 1.5)	−1.2 (−5.3, 2.8)
Total muscle strength (N)	783.2 (32.3)	858.4 (127.7)	**−75.2 (−148.3, −2.0)**	−22.7 (−75.4, 30.0)
Total skin extensibility (mm)	37.7 (0.6)	35.5 (2.8)	**2.2 (0.6, 3.7)**	**2.4 (0.9, 3.8)**
Quantitative bone ultrasound measurements				
BUA (dB/MHz)	57.9 (3.6)	57.6 (14.4)	0.2 (−7.7, 8.2)	2.6 (−5.8, 11.1)
SOS (m/s)	1575.6 (7.1)	1569.8 (23.2)	5.8 (−7.6, 19.2)	2.0 (−12.2, 16.3)
Collagen biochemistry				
Hyp/creatinine (μmol/mmol)	106.1 (6.3)	113.3 (26.7)	−7.1 (−21.6, 7.3)	−7.5 (−22.7, 7.8)
HP/creatinine (μmol/mmol)	250.3 (19.0)	250.9 (69.2)	−0.6 (−38.9, 37.7)	−2.4 (−42.9, 38.1)
LP/creatinine (μmol/mmol)	75.3 (6.8)	74.8 (32.2)	0.5 (−16.7, 17.6)	−2.3 (−20.8, 16.1)
Ratio HP/LP	3.5 (0.2)	3.6 (0.8)	−0.1 (−0.5, 0.3)	−0.01 (−0.4, 0.5)

Values are means (standard error of the mean), unless otherwise indicated.
* Adjustment for age, gender, body height, and body weight. Statistically significant associations were considered reached when 95% CIs did not include the null value and are given in **boldface**.

Our data suggest that reduced urinary cross-links excretion is a co-phenomenon with findings in various organ systems. However, that group differences were not clearly influenced by differences in collagen biochemistry indicates that the latter are not the primary explanation. Still, the most plausible explanation is a natural interindividual variation in connective tissue composition of various tissues. Moreover, the urine parameters of collagen biochemistry are probably not (tissue) specific enough to explain our findings fully. The majority of Hyp, HP, and LP is derived from bone degradation. Thus, a discussion of possible mechanisms with respect to, for example, changes in connective tissue turnover remains speculative. Although connective tissues consist of many different components and subtypes, some organs share the dominance of constituents such as collagen types I and III in vessel walls, joint ligaments, and skin.[33–36] Such shared principal components may partly explain changes in various organs in children with symptoms.

Our findings may have direct clinical implications. We do not know why children with generalized joint hypermobility develop musculoskeletal complaints, whereas other children do not. Our study seems to indicate that symptomatic hypermobile children have more profound hypermobile joints according to the Bulbena criteria[17] and more extensibility of the skin. This may be caused by a more systemic disorder, although no evidence was found for inclusion in the Ehlers-Danlos type III criteria (hypermobile type). A clinical awareness that possible differences in physiology underlie such complaints may lead to changes in clinical approaches in the future. Indeed, current clinical thinking, as apparent from the literature, is driven primarily by the assumption that children are either "normomobile" or "hypermobile," or "hypomobile" for that matter. Genuine collagen disorders, being recognized clinical entities with systemic characteristics, may be considered at one end of the laxity distribution, but when clinical symptoms are present without the characteristics of a collagen disorder, patients still receive diagnoses of specific syndromes, such as benign hypermobility syndrome, on the basis of measurements at the locomotor apparatus only.[13] However, when looking from a broader perspective at patients with locomotor complaints, one might come to an alternative conclusion. Our findings seem more compatible with the view that (hyper)laxity of joints and skin is a component of a natural variation in constitutional laxity of the total body. We suggest that such constitutional laxity of tissues is a graded phenomenon. Our symptomatic group, or patients considered to have benign hypermobility syndrome, may be a subgroup within such a graded scale with manifest collagen disorders at one end. Even among certain types of collagen disorders (Ehlers-Danlos III), there are no clear-cut diagnostic criteria.[37] Obviously, our findings can only be suggestive with respect to possible mechanisms. Additional research into such mechanisms is hampered by the fact that tissue-specific markers of collagen, elastin, and cross-links are not easily available. On the basis of our data we cannot provide evidence that we are dealing with symptomatic joint hypermobility with "normal variability" versus single gene differences.

CONCLUSION

Clinically manifest symptoms in otherwise healthy children with generalized joint hypermobility are accompanied by increases in the laxity of other body

tissues. Thus, generalized joint hypermobility with musculoskeletal symptoms does not seem to be restricted to joint tissues. In symptomatic hypermobile children, a more systemic derangement was also present as compared with asymptomatic hypermobile children. Our results may be compatible with a natural interindividual variation in connective tissue composition as an explanation for different degrees of clinical symptomatology.

ACKNOWLEDGMENTS

The Royal Dutch Society for Physical Therapy provided a grant for biochemical analysis.

We thank M.J.C. Eijsermans, pediatric physical therapist, and M. Riessen, physical therapy student, for logistic support. We also thank the participating children and their parents with symptomatic joint hypermobility and the children from the primary schools Het Spoor and Openbare Montessori School in Zeist, the Netherlands, who served as the reference group.

REFERENCES

1. Raff ML, Byers PH. Joint hypermobility syndromes. *Curr Opin Rheumatol.* 1996;8:459–466
2. Grahame R. Joint hypermobility and genetic collagen disorders: are they related? *Arch Dis Child.* 1999;80:188–191
3. Dalgleish R. The human type I collagen mutation database. *Nucleic Acids Res.* 1997;25:181–187
4. Giunta C, Superti-Furga A, Spranger S, Cole WG, Steinmann B. Ehlers-Danlos syndrome type VII: clinical features and molecular defects. *J Bone Joint Surg.* 1999;81-A:225–238
5. Robinson PN, Godfrey M. The molecular genetics of Marfan syndrome and related microfibrillopathies. *J Med Genet.* 2000;37:9–25
6. Rowe PC, Barron DF, Calkins H, Maumenee IH, Tong PY, Geraghty MT. Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome. *J Pediatr.* 1999;135:494–499
7. Dolan AL, Arden NK, Grahame R, Spector TD. Assessment of bone in Ehlers Danlos syndrome by ultrasound and densitometry. *Ann Rheum Dis.* 1998;57:630–633
8. Wordsworth P, Ogilvie D, Smith R, Sykes B. Joint mobility with particular reference to racial variation and inherited connective tissue disorders. *Br J Rheumatol.* 1987;26:9–12
9. Birrell FN, Adebajo AO, Hazleman BL, Silman AJ. High prevalence of joint laxity in West Africans. *Br J Rheumatol.* 1994;33:56–59
10. Larsson LG, Baum J, Muldolkar GS. Hypermobility: features and differential incidence between the sexes. *Arthritis Rheum.* 1987;30:1426–1430
11. Rikken-Bultman DG, Wellink L, Van Dongen PW. Hypermobility in two Dutch school populations. *Eur J Obstet Gynaecol Reprod Biol.* 1997;77:189–192
12. Grahame R. The hypermobility syndrome. *Ann Rheum Dis.* 1990;49:190–200
13. Grahame R. The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). *J Rheumatol.* 2000;27:1777–1779
14. Gerver WJM, De Bruin R. *Paediatric Morphometrics, a Reference Manual.* Utrecht, the Netherlands: Wetenschappelijke Uitgeverij Bunge; 1996
15. Liebesman JL, Cafarelli E. Physiology of range of motion in human joints: a critical review. *Crit Rev Phys Rehabil Med.* 1994;6:131–160
16. Hogeweg JA, Langereis MJ, Bernards ATM, Faber JAJ, Helders PJM. Goniometry: variability in the clinical practice of a conventional goniometer in healthy subjects. *Eur J Phys Med Rehabil.* 1994;4:2–7
17. Bulbena A, Duro JC, Porta M, Faus S, Vallescar R, Martin-Santos R. Clinical assessment of hypermobility of the joints: assembling criteria. *J Rheumatol.* 1992;19:115–121
18. Bäckman E, Odenrick P, Hendriksson KG. Isometric muscle force and anthropometric values in normal children between 3.5 and 15 years. *Scand J Rehabil Med.* 1989;21:105–114
19. Hogeweg JA, Lemmers D, Temmink P. Skin compliance: measuring skin consistency in the spinal region of healthy children and adults. *Physiother Theory Pract.* 1993;9:205–214
20. Ishimitsu T, Murayama N, Meguro T, et al. Urinary excretions of albumin and type IV collagen in normotensive and hypertensive subjects. *Hypertens Res.* 2000;23:459–466
21. Safar ME, Blacher J, Mourad JJ, London GM. Stiffness of carotid artery wall material and blood pressure in humans: application to antihypertensive therapy and stroke prevention. *Stroke.* 2000;31:782–790
22. Eckert S, Gleichmann U, Zagorski O, Klapp A. Validation of the Omron R3 blood pressure self-measuring device through simultaneous comparative invasive measurements according to the protocol 58130 of the German Institute for validation. *Blood Press Monit.* 1997;2:189–192
23. Njeh CF, Boivin CM, Langton CM. The role of ultrasound in the assessment of osteoporosis. *Osteoporos Int.* 1997;7:7–22
24. Gluer CC, Wu CY, Jergas M, Goldstein SA, Genant HK. Three quantitative ultrasound parameters reflect bone structure. *Calcif Tissue Int.* 1994;55:46–52
25. Van Daele PLA, Burger H, De Laet CEDH. Ultrasound measurement of bone. *Clin Endocrinol.* 1996;44:363–369
26. Beekman B, Verzijl N, Bank RA, von der Mark K, TeKoppele JM. Synthesis of collagen by bovine chondrocytes cultured in alginate: posttranslational modifications and cell-matrix interactions. *Exp Cell Res.* 1997;237:135–141
27. Teerlink T, Tavenier P, Netelenbos JC. Selective determination of hydroxyproline in urine by high-performance liquid chromatography using precolumn derivatization. *Clin Chim Acta.* 1989;183;309–315
28. Silman AJ, Day SJ, Haskard DO. Factors associated with joint mobility in an adolescent population. *Ann Rheum Dis.* 1987;46:209–212
29. Berenson GS, Wattigney WA, Webber LS. Epidemiology of hypertension from childhood to young adulthood in black, white and Hispanic population samples. *Public Health Rep.* 1996;111(suppl 2):3–6
30. Sinaki M. Effect of physical activity on bone mass. *Curr Opin Rheumatol.* 1996;8:376–383
31. Brandt T, Orberk E, Weber R, et al. Pathogenesis of cervical artery dissections: association with connective tissue abnormalities. *Neurology.* 2001;57:24–30
32. Grahame R. Pain, distress and joint hyperlaxity. *Joint Bone Spine.* 2000;67:157–163
33. Riechert K, Labs K, Lindenhayn K, Sinha P. Semiquantitative analysis of type I and III collagen from tendons and ligaments in a rabbit model. *J Orthop Sci.* 2001;6:68–74
34. Kaltsas DS. Comparative study of the properties of the shoulder joint capsule with those of other joint capsules. *Clin Orthop.* 1983;173:20–26
35. Child AH. Joint hypermobility syndrome: inherited disorder of collagen synthesis. *J Rheumatol.* 1986;13:239–243
36. Brull DJ, Murray LJ, Boreham CA, et al. Effect of a COL1A1 Sp1 binding site polymorphism on arterial pulse wave velocity: an index of compliance. *Hypertension.* 2001;38:444–448
37. Murray KJ, Woo P. Benign joint hypermobility in childhood. *Rheumatology.* 2001;40:489–491

Pediatric Generalized Joint Hypermobility With and Without Musculoskeletal Complaints: A Localized or Systemic Disorder?

Raoul H. H. Engelbert, Ruud A. Bank, Ralph J. B. Sakkers, Paul J. M. Helders, Frits A. Beemer and Cuno S. P. M. Uiterwaal

Pediatrics 2003;111;e248
DOI: 10.1542/peds.111.3.e248