Relationship of Generalized Joint Hypermobility With Vesicoureteral Reflux and Urinary Tract Infection

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Original Paper

Introduction. Generalized joint hypermobility is deemed to be an underlying risk factor for many clinical conditions. The goal of this study was to determine the prevalence of generalized joint hypermobility in patients with vesicoureteral reflux.

Materials and Methods. This was a cross-sectional study on 313 children, 3 to 15 years old, with a history of urinary tract infection. Generalized joint hypermobility was evaluated according to the Beighton scores. Urinary tract ultrasonography and cystography were done if indicated. Participants were divided into 2 groups, group 1 without urinary tract abnormality and group 2 with primary vesicoureteral reflux, which were compared with the control group.

Results. Generalized Joint hypermobility was documented in 37.2% of the children in the control group and 45.7% of those in group 1 ($P = .25$). This rate was 62.3% in group 2 ($P < .001$ compared to controls; odds ratio, 2.79; 95% confidence interval, 1.61 to 4.82). Generalized Joint hypermobility was seen in 44.1% of the children with mild VUR, 60.5% of those with moderate VUR, and 86.2% of those with severe VUR. There was a significant relationship between the hypermobility incidence and the urinary reflux severity ($P = .003$).

Conclusions. This study showed the prevalence of GJH in children with VUR was more than that in the general population, and the prevalence of hypermobility syndrome increased with the reflux severity.

INTRODUCTION

A hypermobile joint is a joint whose motion range is above normal regarding age, sex, and race. Studies in various population show that generalized joint hypermobility (GJH) is more common in women and children, and its prevalence decreases as age increases.[1] Epidemiologic studies have reported its prevalence to be up to 35% for men and 57% for women.[2] It seems that GJH is a collagen disorder which is caused by a defect in the collagen structure or a change in collagen subtypes.[3] Higher prevalence of generalized joint laxity in monozygotic twins compared to dizygotic twins indicates a genetic component.[4] Generalized joint hypermobility is observed in several connective tissue disorders such as Marfan syndrome, Ehlers-Danlos Syndrome, and osteogenesis imperfecta. Also, it is observed in genetic disorders such as Down syndrome as well as metabolic diseases such as homocysteinuria and hyperliperlysinemia. At the same time, it is common among the healthy people with no particular problem.

The association of GJH has already been reported with some diseases such as arthralgia, soft tissue lesion, recurrent joint dislocation or subluxation, anxiety, carpal tunnels syndrome, vesicoureteral reflux (VUR), urinary tract infection (UTI), mitral valve prolapse, stria gravidarum, varicose vein formation, and abdominal herniation.[3,5-9] In a study performed by van Eerde and colleagues,[9] the relationship between hypermobility and VUR was studied, in which the Bulbena scale score was used to evaluate hypermobility. In this study, the prevalence of hypermobility in the patients with VUR was more than that of the control group. Since the laxity might correlate with the mechanical opening and closing of the sphincter, the aim of this study was to investigate the association of urinary reflux and urinary infection with GJH.

MATERIALS AND METHODS

This cross-sectional study was conducted from April 2010 to April 2011 in Loghman-Hakim Hospital, in Tehran. Children aged 3 to 15 years who attended the pediatric clinic and had documented UTI by urinalysis and urine culture were included in the study. The exclusion criteria were a history of treated VUR, Marfan syndrome, William syndrome, structural anomaly of the urinary system (including ureteropelvic stenosis, ureterovesicular obstruction, neurologic bladder or duplex system), homocysteinuria, and rheumatologic diseases. In addition, gymnasts and patients for whom cystography was not indicated were not included. Since the prevalence of VUR in the general population is only 1%, the control subjects were selected in accordance with age and sex among the children who were visited at this center due to common cold and had no record of UTI or other renal problems and did not have a history of VUR in their siblings and parents. All of the participants' parents provided informed consent.

The participants were visited and scored by a pediatrician who had been trained in hypermobility evaluation using the Beighton scoring method (Table 1) and was unaware of the patient's chief complaint. The defining cutoff point of GJH is set to a value from 3 and greater to 6 and greater.[10] For this study, the criterion was set as greater than or equal to 5. Participants' demographic and clinical characteristics, including age, sex, history of previous UTI, and history of treated VUR were recorded. Urinary ultrasonoghraphy was done for all, while cystography was done only for children of any age with 2 or more febrile UTI episodes and children of any age with a first febrile UTI who had a family history of renal or urologic disease, poor growth, hypertension, or abnormal urinary tract on ultrasonography. Standard voiding cystoureterography was done for the boys, and direct radio nuclear cystography was done for the girls. A grade I reflux on standard cystography was equivalent to the mild degree in nuclear cystography; grades II and III were equivalent to the moderate degree in nuclear cystography, and grades IV and V were equivalent to severe degree in nuclear cystography.

Participants who did not have VUR were categorized in group 1 and those who had VUR, in group 2. Overall, 360 children participated in this study, including 120 children in groups 1 and 2 and the control group. Data analysis was performed by the SPSS software (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, Ill, USA). Continuous data were analyzed by the Kolmogorov-Smirnov test for normality distribution. All quantitative data were reported as mean ± standard deviation and analyzed using the Student t test or the Mann-Whitney U test, where appropriate. For comparisons between 3 groups, the analysis of variance and the Tukey test were applied. Qualitative data were reported as frequency and percentage and analyzed using the

Table 1. The Nine-point Beighton Hypermobility Score

Ability	Score		
	Right Side	Left Side	Both Sides
Oppose the thumb to the volar aspect of the ipsilateral forearm	1	1	…
Passively dorsiflex the fifth metacarpophalangeal joint to ≥ 90°	1	1	…
Hyperextend the elbow to ≥ 10°	1	1	…
Hyperextend the knee to ≥ 10°	1	1	…
Place hands flat on the floor without bending the knee	…	…	1

chi-square and Fisher exact test, where appropriate. A *P* value less than .05 was considered significant, and 95% confidence intervals (CIs) were calculated for adjusted odds ratios (ORs).

RESULTS

After considering the exclusion criteria, 92 children remained in group 1 and 106 in group 2. Of the controls, 113 children completed the study. Baseline characteristics of the participants in the three groups are shown in Table 2.

The mean Beighton scores are shown in Table 3. There was a significant difference only between the control group and group 2 ($P < .001$). Generalized joint hypermobility was documented in 42 children (45.7%) in group 1, 66 (62.3%) in group 2, and 18 (37.2%) in the control group. There was no significant difference between the hypermobility incidence rates between the control and group 1 ($P = 0.25$; OR, 1.42, 95% CI 95%, 0.81 to 2.49), but there was a significant difference between the hypermobility incidence rates of the controls and group 2 ($P < .001$, OR, 2.79; 95% CI, 1.61 to 4.82) and between groups 1 and 2 ($P = 0.02$; OR, 1.96; 95% CI, 1.11 to 3.47).

Of the children with UTI as well as VUR, 80 had unilateral reflux and 26 had bilateral reflux. Among those who had unilateral reflux, 60% (n = 48) had hypermobility, too, while 69% (n = 18) of those who had bilateral reflux had hypermobility. There was no significant relationship between unilateral or bilateral VUR and the hypermobility incidence rate in this group ($P = .49$; Figure 1).

The mean Beighton scores were 4.47 ± 2.73 in the children with mild VUR, 5.16 ± 2.84 in the patients with moderate VUR, and 6.62 ± 2.46 in those with severe VUR. There was a significant relationship between the average Beighton scores

and the severity of reflux ($P = .007$; Figure 2).

Fifteen child with mild VUR (44.1%), 26 with moderate VUR (60.5%), and 25 with severe VUR (86.2%) had hypermobility. There was a significant relationship between the hypermobility incidence and the VUR severity ($P = .003$; Figure 3).
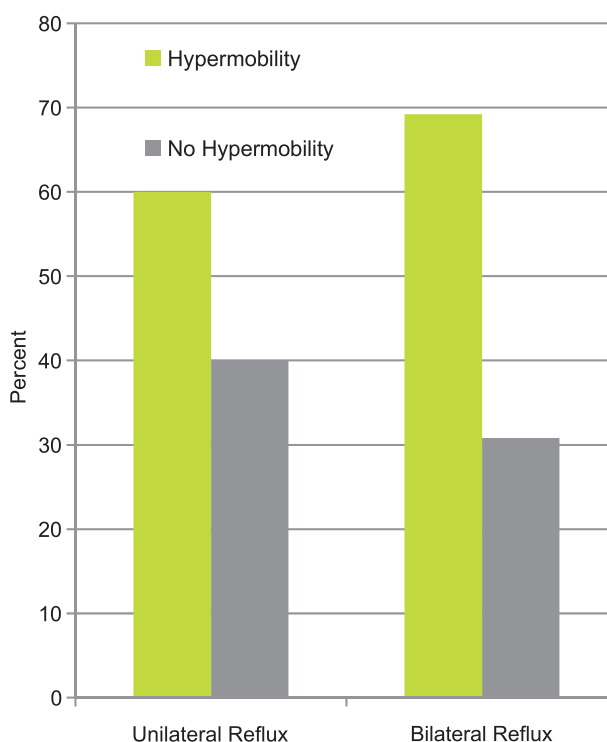

Figure 1. Distribution of the incidence of hypermobility by unilateral or bilateral urinary reflux in children with urinary tract infection.
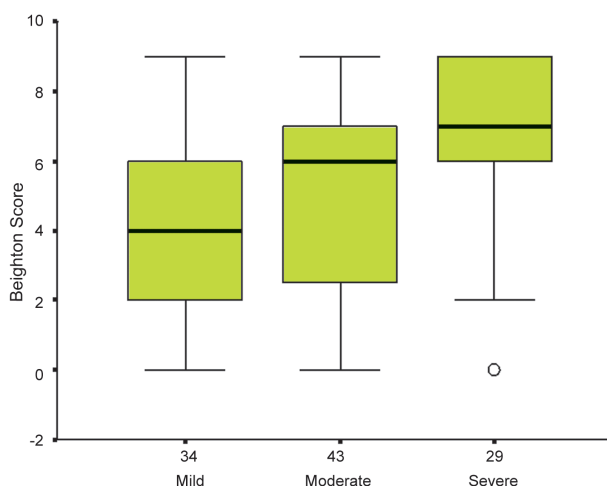

Figure 2. Distribution of Beighton scores in terms of reflux severity in the children visiting Loghman-Hakim Hospital with urinary tract infection

Table 2. Baseline Characteristics of Participants

Characteristic	Group 1	Group 2	Control	*P*
Mean age, y	5.9 ± 2.7	5.3 ± 2.5	6.3 ± 3.2	.05
Sex				
Male	9	10	14	
Female	83	96	99	.70

Table 3. Mean Beighton Scores of Participants

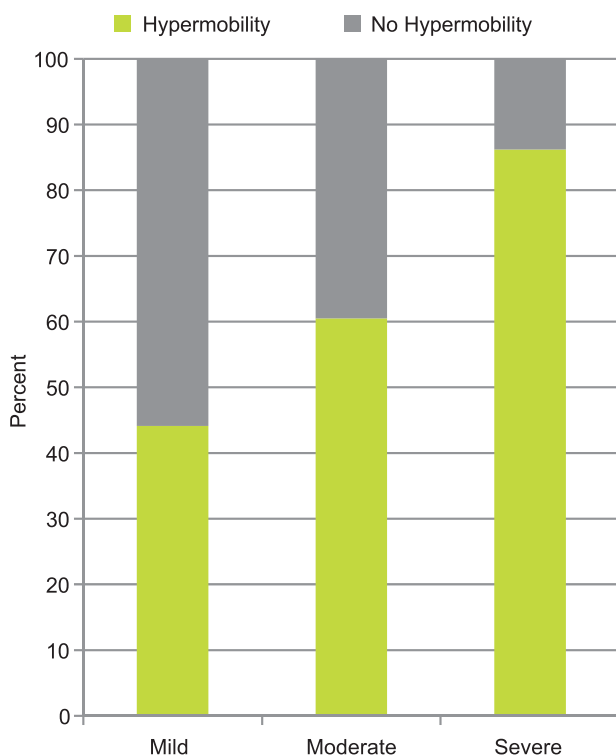| Characteristic	Group 1	Group 2	Control	*P*
Beighton score	4.7 ± 2.8	5.3 ± 2.8	3.9 ± 2.9	< .001

Figure 3. Distribution of the incidence of hypermobility by severity of urinary reflux among the children with urinary tract infection

DISCUSSION

In this study, we evaluated the GJH according to the Beighton scores among the patients with UTI, with or without VUR, and compared them with the control group. The prevalence of GJH in the group with UTI without VUR had no difference with the control group, while its prevalence in the group with UTI and VUR was more than the control group as well as the UTI without VUR group. Although there was no significant relationship between unilateral or bilateral VUR and the incidence of GJH, the prevalence of hypermobility increased with the reflux severity. One of the advantages of our study is that the assessors were not aware of the patient's history, and that the relationship of hypermobility and UTI, with or without reflux, was studied. The limitation of this research is that the voiding symptom and also symptomatic hypermobility were not considered in these patients; ie, the benign joint hypermobility syndrome was not separated from the group with no muscloskeletal symptom.[11,12]

In a study performed on the children with benign joint hypermobility syndrome, the prevalence of UTI was 13% in girls and 6% in boys (in comparison to 2% to 5% in the normal children), and the VUR prevalence was 3 times as high as the normal population.[8] This research was not consistent with our study, with regards to high UTI prevalence rate, which could be due to not considering the presence of reflux in the children with UTI in this research. In a study performed by van Eerde and colleagues,[9] the relationship between hypermobility and VUR was studied, in which the Bulbena score was used to evaluate hypermobility. The results of this study were consistent with our study, such that the prevalence of hypermobility in the patients with VUR was more than the control group and it was increasing with reflux severity. However, in this study, the sample size was low and the relationship of hypermobility and UTI with or without VUR was not evaluated separately.

Urinary tract infection in GJH could be due to presence of defecation dysfunctions, such as constipation, fecal soiling, and lower urinary tract dysfunction (urinary incontinence in these patients).[13,14] Since GJH is a connective tissue disorder which causes the joint ligament laxity, the association of GJH and VUR could be due to structural changes in the connective tissue of the ligament of patients with GJH and the connective tissue of the pelvic floor and the bladder and ureter.[15] Such that the higher ratio of the type 3 collagen to the type 4 collagen and also the genetic alternation in the collagen metabolism is reported in the patients with hypermobility.[3] Yet in a study conducted by Lee and coworkers, the increase in the type 3 collagen was verified in the refluxing ureter.[16]

In the study conducted by Change and colleagues, deposition and abnormal arrangement of type 3 collagen was blamed for bladder dysfunction.[17] The role of change in the extracellular matrix composition in GJH and VUR is verified in some studies. In the study conducted by Zweers and associates, it is shown that heterozygous tenascin-x gene mutation or deletions causes the lack of some matrix protein, named tenascin-x, in the patients with GJH.[18] Also, in other studies, the effect of extracellular matrix remodeling and change in the ratio of collagen to smooth muscle in the refluxing ureter is shown, which causes structural and functional changes in the valve and deterioration of its operating mechanism.[19,20]

Since the role of collagen in the incidence of urinary reflux as well as hypermobility is verified, a genetic interrelationship between these two can be considered as the cause for their association.[21-25]

Another factor which has been associated with GJH and VUR is the displacement of the location of the ureteral orifice in the bladder in patients with hypermobility.[9] Considering this study and other similar reports, it seems that study of the causal association of these two could be the basis for remarkable studies in the future.

CONCLUSIONS

This study showed the prevalence of GJH in children with VUR was more than that in the general population, and the prevalence of hypermobility syndrome increased with the reflux severity.

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CONFLICT OF INTEREST

None declared.

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