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A Novel Radiological Sign Associated with Vesicoureteral Reflux and Urinary Bladder Volume in Children: A Clinical Study

Çocuklarda Vezikoüreteral Reflü ve Mesane Volümüyle İlişkili Yeni Bir Radyolojik Belirti: Klinik Çalışma

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ABSTRACT Objective: The aim of the current study was to investigate demographic, clinical and radiological factors prone to influence urinary bladder volume in vesicoureteral reflux with special attention to hypoplasia of the 5th lumbar vertebra. **Material and Methods:** This retrospective study was performed using data derived from pediatric patients who were admitted to the pediatric urology department of our tertiary care center between 2010 and 2015 with complaints consistent with vesicoureteral reflux. A total of 104 children were subgrouped into two according to age (<72 months and ≥72 months). Demographic data, clinical findings, radiological data including hypoplasia of the fifth lumbar vertebra and results derived from voiding cystourethrogram, scintigraphy and ultrasonography were gathered and analyzed. **Results:** In children <72 months, incidence of vesicoureteral reflux was remarkably higher and volume of urinary bladder was significantly increased in children with diminished height of 5th lumbar vertebra corpus (p<0.001). On the other hand, findings derived from scintigraphy and ultrasonography were not different in patients with diminished height of 5th lumbar vertebra corpus. In children ≥72 months, frequency of vesicoureteral reflux was notably higher in children with lower height of vertebral body corpus (p=0.001). However, there was no difference between children with normal and decreased 5th lumbar vertebra corpus in terms of urinary bladder volumes (p=0.970). **Conclusion:** We suggest that hypoplasia of 5th lumbar vertebra can be a novel and practical radiological clue that may aid in the diagnosis of vesicoureteral reflux in children. However, further controlled trials on larger series are essential for understanding its clinical significance.

Keywords: Vesicoureteral reflux; vertebral body; urinary bladder

ÖZET Amaç: Bu çalışmanın amacı, 5. lomber vertebra hipoplazisine özellikle dikkat ederek vezikoüreteral reflüde mesane volümünü etkilemeye eğilimli demografik, klinik ve radyolojik faktörleri araştırmaktır. **Gereç ve Yöntemler:** Bu retrospektif çalışmada, 2010-2015 yılları arasında 3. basamak sağlık merkezimizin çocuk ürolojisi bölümüne vezikoüreteral reflüye uyumlu yakınmalarla kabul edilen çocuk hastalar çalışmaya dâhil edilmiştir. Toplam 104 çocuk yaşa göre 2 alt gruba (<72 ay ve ≥72 ay) ayrılmıştır. Demografik veriler, klinik bulgular ve 5. lomber vertebra hipoplazisini de içeren radyolojik veriler, işeme sistoüretrografisi, sintigrafi ve ultrasonografi sonuçları toplanmış ve analiz edilmiştir. **Bulgular:** Yetmiş iki aydan küçük, 5. lomber vertebra cisminin yüksekliği azalmış çocuklarda vezikoüreteral reflü insidansı belirgin derecede yüksekti ve üriner mesane volümü anlamlı derecede artmıştı (p<0,001). Diğer taraftan sintigrafi ve ultrasonografiden elde edilen bulgular 5. lomber vertebra cismi azalmış hastalarda farklı değildi. Yetmiş iki aylık veya daha büyük, vertebra cismi yüksekliği daha düşük çocuklarda vezikoüreteral reflü sıklığı belirgin derecede daha yüksekti (p=0,001). Ancak mesane volümleri açısından 5. lomber vertebra cismi normal ve azalmış çocuklar arasında herhangi bir farklılık yoktu (p=0,970). **Sonuç:** Beşinci lomber vertebra hipoplazisinin çocuklarda vezikoüreteral reflü tanısına yardımcı olabilen yeni ve pratik bir radyolojik ipucu olduğunu düşünmekteyiz. Ancak bunun klinik önemini anlamak için daha geniş serilerde kontrollü çalışmaların yapılması gereklidir.

Anahtar Kelimeler: Vezikoüreteral reflü; vertebral cisim; mesane

Vesicoureteral reflux (VUR) is a condition consisting of the retrograde passage of urine from the bladder into the ureter and up to the renal pelvis in severe forms.[1] It is identified as the principal cause

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of chronic kidney disease in Turkey.[2] Principles of management are based on prevention of injury and structural changes of urinary tract as well as reduction of morbidity during treatment and follow-up.[3,4]

It is known as a significant and possibly avoidable cause of chronic renal insufficiency and end-stage renal failure in adults and children. The objectives of the treatment are the correction of the anatomical defect and prevention of the renal damage. Several efforts have been devoted to early identification of VUR. Nevertheless, there are major debates on the need for screening methods, the function of medical vs surgical treatment, timing of elective surgery and duration of antibiotic prophylaxis.[1]

Voiding cystourethrography (VCUG) is recognized as the gold standard for the diagnosis of VUR; but this method exposes the patient to radiation and includes catheterization, that rises infection risk.[5] In numerous studies, the ways to avoid the use of VCUG in children with urinary tract infection have explored, but there is still no general agreement on an approach for optimally diagnosing VUR in this group of patients.[6,7] Hence, prenatal screening using ultrasonography can be useful for identification of fetuses with dilated pelvis and possible VUR. On the other hand, the definition of a cut-off point of fetal pelvic diameter for further assessment with VCUG is still controversial.[1] Improvement of diagnostic methods and a meticulous assessment of landmarks is important to avoid unnecessary diagnostic and therapeutic interventions.

VUR frequency varies significantly between age groups in children and there is a noteworthy difference between children <72 months of age (70%) and children ≥72 months of age (25%).[8]

Vertebral hypoplasia is determined in about 5% of population and it may be accompanied by low back pain and urinary system disorders.[9] In the current study, we propose hypoplasia of 5th lumbar vertebra as a novel radiological sign that may be useful in identification of children with VUR.

We investigated the demographic, clinical and radiological factors prone to influence urinary bladder volume in children suffering from VUR with special attention to vertebral hypoplasia involving the fifth lumbar vertebra. Our purpose was to seek whether hypoplasia of the fifth lumbar vertebra could be a useful marker in the diagnosis of VUR.

MATERIAL AND METHODS

Study Design: This retrospective study was performed after the approval of local institutional review board (dated: 11.03.2015, no: 73799008). A total of 104 cases (56 females, 48 males) who were referred to the radiology department of our institution for VCUG due to suspicion of VUR between March 2010 and May 2015. Patient consent was not required at that time for review of medical records. The study has been conducted in accordance with the principles of the Helsinki Declaration.

Diagnosis of VUR was confirmed with VCUG and results yielded that 21 children (20.2%) had VUR. The average ages of patients with VUR and without VUR were 39.5±42.83 months and 53.9±39.79 months, respectively. No difference was detected between patients with VUR and without VUR in terms of age (p=0.053) and sex distribution (p=0.086). Owing to the physiological maturation interval of urinary bladder, the children were subdivided into two groups with respect to age and children <72 months (n=82) and ≥72 months (n=22) were evaluated distinctly.

Relationship between demographic, anatomical and radiological features to diagnosis of VUR and urinary bladder volume was investigated. In this purpose, age, gender, height of 5th lumbar vertebra corpus, ultrasonographic features of kidney, bladder morphology, indications for referral of the patient and scintigraphic findings (normal/pathological) were noted.

The same radiologist who is experienced in urogenital system imaging has evaluated the views for morphological changes in urinary bladder, kidney, and lumbar vertebra. Children with spina bifida or neurogenic bladder were excluded from the study.

"L5 hypoplasia" diagnosis was confirmed with the help of oblique and lateral control fluoroscopic images taken during VCUG. When L5 vertebra cor-

pus was compared with the L4 vertebra corpus, "L5 hypoplasia" was considered if the shapes of both corpora are the same and height of L5 vertebra corpus was reduced at least by 5%.[10,11]

Frequency of VUR in cases with various demographic, anatomical and radiological features was compared and factors prone to influence the volume of urinary bladder were investigated. Scintigraphy was performed by the nuclear medicine department to evaluate the renal function. Ultrasonography was implemented using a Toshiba Applio XV device (Toshiba Medical Systems Corporation, Otawara-shi, Tochigi-ken, Japan). Voiding cystourethrogram was carried out after indication was established and urethral sounding was made by the clinician. Bladder capacity was measured and presence of VUR was sought during filling of the bladder and micturition as described in the literature.[12-14] Radioopaque fluid was introduced into the urinary bladder until the estimated bladder volume was reached as for the following formulae. For children younger than 1 year, the formula proposed by Holmdahl was employed: Bladder capacity = [2.5 x age (months)] + 38.[12] For children older than 1 year, the calculation was based on the formula suggested by Koff et al. as follows: Bladder capacity = [2 + age (years)] x 30.[13] The occurrence of VUR was observed until the calculated volume.

Urinary cultures were obtained 1 week before filling the bladder. In case of infection, the procedure was delayed for 1 week after initiation of appropriate treatment. Patients were evaluated again at the end of the treatment for urinary tract infection. Urine collection was started 2-3 hours before the procedure which was carried out by 2 experienced nurses. After administration of antiseptic solution to perineal region, bladder was filled with 6F double-lumen catheter. Isotonic saline was given at 25-36 °C under sterile conditions and at a rate of filling 10% of bladder capacity not earlier than 1 minute. The bladder volume was performed using ultrasonography as described by Dicuio et al.[15]

In addition to descriptive parameters including age and gender, ultrasonographic findings such as hydronephrosis, atrophy, pelvic ectasia, nephrocalcinosis, horseshoe kidney and unilateral renal agenesis were recorded. Thickness and echogenicity of the renal parenchyma as well as structural abnormalities of urinary bladder like trabeculations or diverticulae have been considered.

STATISTICAL ANALYSIS

In the data analysis, IBM Statistical Package for Social Sciences (SPSS) Statistics 20 software (*SPSS Inc., Chicago, IL, USA*) was used. Kolmogorov Smirnov test was applied to test the normality of distribution for variables. Variables having normal distribution were assessed with parametric methods, while non-parametric methods were used for evaluation of variables without normal distribution. Pearson correlation test was used to evaluate correlation between variables. Comparison of categorical variables was accomplished using Pearson Chi-square or Fisher's Exact tests. Mann-Whitney U test was used for comparison of 2 independent groups, while Kruskal-Wallis test was performed to compare more than 2 groups. Comparison of categorical variables was made with Exact method for Pearson Chi-square test. Quantitative data were signified as median and interquartile range (IQR). Confidence interval was 95% and level of significance was set at p value <0.05.

RESULTS

The data derived from children <72 months of age are shown in Table 1, while information gathered from children ≥72 months can be seen in Table 2, respectively. The average age in the whole study group was 42.0±43.5 (range, 1 to 194 months). In children <72 months of age, 15 had been diagnosed with VUR and of these 15 cases, 9 were bilateral, while 6 were unilateral. In children ≥72 months of age, 6 were diagnosed with VUR. Of these 6 cases, 4 were bilateral and 2 were unilateral.

Children with and without vertebral hypoplasia had similar age (p=0.058) and sex distributions (p=0.726). In children younger than 72 months, VUR positivity was detected in 15 (18.3%) out of 82 cases. Eight (53.3%) of these 15 children had a hypoplastic 5th lumbar vertebra. In 67 children without VUR, only 2 (3%) had hypoplastic lumbar vertebra. This difference was significant (p<0.001) indicating that VUR

positivity was more likely to exist in children with hypoplastic lumbar vertebra. Similarly, urinary bladder volume in children with hypoplastic lumbar vertebra (median-interquartile range: 250.0-132.5) was notably higher than that in children with normal lumbar vertebra (median-interquartile range: 90.0-80.0) and this difference was also statistically significant (p<0.001) (Pearson Chi-square test, Fisher's Exact Test) (Table 1).

In contrast, scintigraphic data (expressed as normal/pathological) and ultrasonographic data (indicating pelvic ectasia, hydronephrosis, atrophy, horseshoe kidney, calyceal ectasia) (p=0.191 for right side; p=0.105 for left side) did not display any notable differences in children with and without 5th lumbar vertebral hypoplasia in patients <72 months of age. In this subgroup of patients, no difference was noted between children with and without 5th lumbar vertebral hypoplasia in terms of urinary bladder volume (p=0.970), scintigraphic findings on right (p=0.258) and left (p=0.340) sides, parenchyme thickness on right (p=1.00) and left sides (p=0.169) and parenchyme echogenicity on right (p=0.230) (Pearson Chi-square test, Fisher's Exact Test) (Table 1).

For children ≥72 months of age, frequency of VUR in 6 cases with hypoplastic lumbar vertebra was 83.3%, while it was 6.2% in 16 children with normal 5th lumbar vertebra (p=0.001). This difference was noteworthy reminding that children with hypoplastic 5th lumbar vertebra may have an increased likelihood of VUR compared to children with normal 5th lumbar vertebra. In contrast, urinary bladder volumes (p=0.970), scintigraphic findings on right (p=0.646) and left sides (p=0.309), parenchyme thicknesses on right (p=1.00) and left sides (p=0.169) and parenchyme echogenicity on right (p=1.00) and left (p=0.481) were not statistically different in children with normal and hypoplastic 5th lumbar vertebra (Pearson Correlation test, Mann-Whitney U test, Kruskal-Wallis test) (Table 2).

Figure 1 demonstrates a loss of height in 5th lumbar vertebra compared to that of 4th lumbar vertebra in a 4 -year and 3-month-old child. Figure 2 displays a VCUG indicating a grade 4 VUR on right side in the same patient.

DISCUSSION

The present study was implemented to evaluate the diagnostic value of hypoplasia of 5th lumbar vertebra

TABLE 1: Clinical and radiological characteristics with respect to developmental status of 5th lumbar vertebra in children <72 months.

Parameter			5th lumbar vertebra		
			Normal (n=72)	Hypoplastic (n=10)	p value
Urinary bladder volume			90.0±80.0	250.0±132.5	<0.001*
Vesicoureteral reflux	Present		7 (9.7%)	8 (80%)	<0.001*
	Absent		65 (90.3%)	2 (20%)	
Scintigraphy	Right side	Missing information	17 (23.6%)	2 (20%)	0.258
		Normal	47 (65.3%)	5 (50%)	
		Pathologic	8 (11.1%)	3 (30%)	
	Left side	Missing information	19 (26.4%)	2 (20%)	0.340
		Normal	44 (61.1%)	5 (50%)	
		Pathologic	9 (12.5%)	3 (30%)	
Parenchyme thickness	Right side	Normal	71 (98.6%)	9 (90%)	0.230
		Thin	1 (1.4%)	1 (10%)	
	Left side	Normal	72 (100%)	10 (100%)	-
		Thin	0	0	
Parenchyme echogenicity	Right side	Normal	67 (93.1%)	10 (100%)	1.00
		Thin	5 (6.9%)	0	
	Left side	Normal	66 (91.7%)	9 (90%)	1.00
		Thin	6 (8.3%)	1 (10%)	

Abbreviations: *Statistically significant.

TABLE 2: Clinical and radiological characteristics with respect to developmental status of 5th lumbar vertebra in children ≥72 months.

Parameter			5th lumbar vertebra		
			Normal (n=16)	Hypoplastic (n=6)	p value
Urinary bladder volume			275.0±187.5	275.0-237.5	0.970
Vesicoureteral reflux	Present		1 (6.2%)	5 (83.3%)	0.001*
	Absent		15 (93.8%)	1 (16.7%)	
Scintigraphy	Right side	Missing information	2 (12.5%)	1 (16.7%)	0.646
		Normal	8 (50%)	4 (66.7%)	
		Pathologic	6 (37.5%)	1 (16.7%)	
	Left side	Missing information	4 (25%)	1 (16.7%)	0.309
		Normal	7 (43.8%)	1 (16.7%)	
		Pathologic	5 (31.2%)	4 (66.7%)	
Parenchyme thickness	Right side	Normal	14 (87.5%)	5 (83.3%)	1.00
		Thin	2 (12.5%)	1 (16.7%)	
	Left side	Normal	15 (93.8%)	4 (66.7%)	0.169
		Thin	1 (6.2%)	2 (33.3%	
Parenchyme echogenicity	Right side	Normal	13 (81.2%)	5 (83.8%)	1.00
		Thin	3 (18.8%)	1 (16.7%)	
	Left side	Normal	15 (93.8%)	5 (83.8%)	0.481
		Thin	1 (6.2%)	1 (16.7%)	

Abbreviations: *Statistically significant.

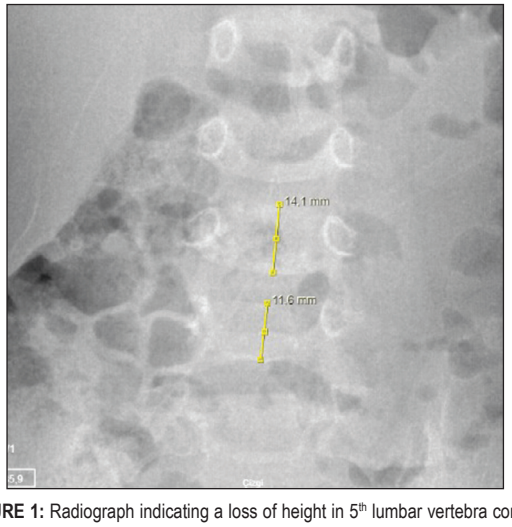

FIGURE 1: Radiograph indicating a loss of height in 5th lumbar vertebra compared to that of 4th lumbar vertebra in a 4-year and 3-month-old child.

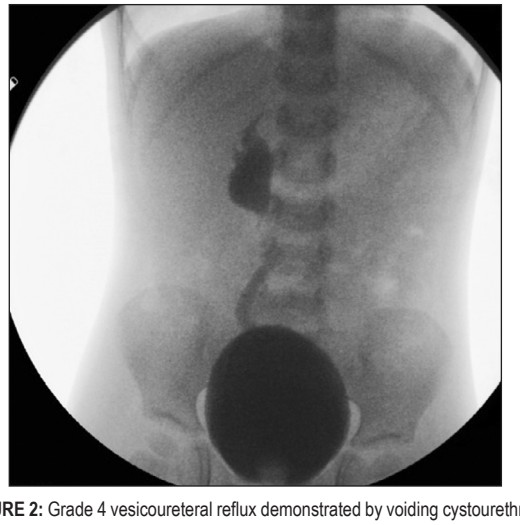

FIGURE 2: Grade 4 vesicoureteral reflux demonstrated by voiding cystourethrography on the right side of a patient.

in children with VUR and to investigate whether there is an association of hypoplasia of 5th lumbar vertebra with clinical and radiological variables.

Vertebral hypoplasia in lumbosacral region is detected in 5% of population and it mainly involves the fifth lumbar vertebra.[9] These patients may present with complaints including low back pain and urinary system disorders.[9]

Our results yielded that VUR is more frequently observed in case of 5th lumbar vertebral hypoplasia. In addition, urinary bladder volume is higher in these children if they are younger than 72 months of age. Even though further studies are warranted for evaluation and validation of hypoplasia of 5th lumbar vertebra as a novel marker for VUR and urinary tract pathologies, we suggest that our results are promising

and may open new horizons in terms of exploration of new and reliable radiological clues.

Causes of primary VUR may be attributed to incompetency of the ureterovesical junction valve mechanisms and increased intravesical pressure. These alterations lead to several anatomical distortions predisposing to VUR.[13] Infants with VUR are mostly only investigated with VCUG rather than urodynamics, the question arises to if there are any radiological signs that may aid in earlier diagnosis of VUR. Reflection of signs including low bladder capacity, high voiding pressure and dyscoordination of voiding to imaging modalities is not very well established.[16]

Timely diagnosis is especially important in VUR, since it may lead to serious morbidity such as bladder dysfunction, hydronephrosis and recurrent urinary tract infection. Delayed diagnosis may result in more severe clinical presentations including renal scarring, renal failure, hypertension, and low rates of resolution.[3,17]

Spontaneous resolution of VUR depends on the age, gender, initial grade of VUR and bladder volume at the onset, presence of renal scarring, and voiding dysfunction.[18] High grade VUR has been linked with higher risk of pyelonephritis and renal scarring as well.[18] Discrimination of cases likely to have spontaneous resolution is another important issue, since our study is not designed prospectively involving the follow-up of patients, it is impossible to draw any conclusions on the use of lumbar vertebral hypoplasia. Further trials focusing on this topic may reveal its implications thoroughly.

In conjunction with our results, Sjöström et al. have suggested that urinary bladder capacity and residual urine were higher with increasing grade of VUR.[19] We did not come across any scintigraphic evidence supporting that children with hypoplastic lumbar vertebra were prone to more injury due to VUR. This is contradictory to the report by Park et al. who stated that VUR was linked with a higher rate of urinary tract infection leading to chronic renal damage.[20] The lack of data for VUR grades in our series as well as resolution of VUR in patients with scintigraphic pathology may be possible causes for this difference.

Infants with larger bladder capacities are supposed to have high-grade VUR and estimation of bladder capacity accurately is an important aspect in these cases of children with VUR.[3] We noted that hypoplastic lumbar vertebra was associated with likelihood of VUR and increased volume / capacity of urinary bladder in children <72 months. In children older than 72 months of age, an increased rate of diagnosis of VUR -without any difference reflected in the volume of urinary bladder- was established in the presence of hypoplastic lumbar vertebra. The bladder capacity was measured using a formula which is relatively less affected by factors such as age and growth.[14]

Knudson et al. suggested that urinary bladder volume was higher at onset of VUR and age less than 2 years as well as prenatal diagnosis can be independent variables for resolution of VUR resolution.[21]

No remarkable scintigraphic or ultrasonographic clues could be detected accompanying VUR and hypoplasia of lumbar vertebra. This is interesting since hypoplasia of lumbar vertebra can be an early sign that may aid in diagnosing VUR before hydronephrosis and other sequelae occur. Evaluation of radiological findings and integration with clinical data is mandatory to set up an appropriate treatment and follow-up strategy in children with VUR.

Majority of the radiological signs accompanying increased activity in the bladder detrusor are nonspecific to VUR and are seen mainly during early childhood.[17,22] In our series, urinary bladder wall abnormalities such as trabeculations or diverticula formation were not linked with hypoplastic lumbar vertebra. These structural alterations may be partially due to immature or overactive contractions unrelated with VUR.[20]

To avoid hazardous consequences of VUR in children, enhancement of diagnostic methods is crucial. From this point of view, we imply that assessment of lumbar vertebra together with other diagnostic measures may decrease the need for more invasive procedures especially in the early stage of disease. Results of our present study imply that hypoplasia of lumbar vertebra can be an early sign for ruling in VUR in the absence of remarkable alterations in ultrasonography and scintigraphy.

Limitations of the current study include the comparatively small sample size, lack of standardi-

zation of data derived from a single institution, lack of homogeneity of age distribution, lack of grading of VUR, and possible impacts of ethnic, environmental, and genetic factors. Moreover, the patients presented in a wide age spectrum and VUR is a disease which may spontaneously recover over time. Therefore, some patients with previous history of VUR may seem to be normal at the time of admission.

CONCLUSION

Our preliminary results imply that hypoplasia of 5th lumbar vertebra can be a novel and practical radiological clue that may aid in the diagnosis of VUR in children. This may aid in timely diagnosis and effective management of VUR, as well as prevention of complications and morbidities. Further studies are required for understanding the clinical significance hypoplasia of 5th lumbar vertebra in children with VUR, and for understanding the relationship between lumbar vertebral hypoplasia and VUR.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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