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Is there an association between histopathological changes in the lower ureter and renal functions? Evaluation of patients who underwent ureteroneocystostomy for ureterovesical obstruction or vesicoureteral reflux

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Background/aim: We aimed to assess the relationship between the histological changes of the ureterovesical junction (UVJ) and renal functions. Therefore, we evaluated histological changes of the lower ureter and renal scintigraphy findings of patients for whom ureteroneocystostomy was performed because of vesicoureteral reflux (VUR) or ureterovesical junction obstruction (UVO).

Materials and methods: UVJ specimens were obtained from 18 children. We investigated the changes in neuronal innervation, muscular morphology, extracellular matrix, and apoptosis rate with renal scintigraphy findings.

Results: Seven UVO and 11 VUR patients were treated. Alpha-actin expression in smooth muscle cells was found to be lower ($P < 0.001$) while neuronal defect was more prominent in the UVO group ($P = 0.002$). The renal functions decreased as the smooth muscle structural defect increased in the VUR group ($P < 0.05$).

Conclusion: Neuronal tissue and muscle tissue were more defective in the UVO group. The decrease in neuronal fibers and muscle cells explains the pathogenesis of the obstructive group, but no difference was observed regarding the accumulation of collagen type 3 and cellular apoptosis between the VUR and UVO groups. In the VUR group, renal functions decreased while the smooth muscle defect at the distal end of the ureter increased.

Key words: Obstructive uropathy, immunohistochemistry, S-100, alpha-smooth muscle actin

1. Introduction

The morphological or histological abnormalities of the lower ureter lead to various pathological entities. Vesicoureteral reflux (VUR) and ureterovesical junction obstruction (UVO) are the most common (1). The early diagnosis and treatment of both pathologies are important as they can cause hypertension and end-stage renal failure (2–6).

In the literature, there is no study that compared the renal function of the upper urinary system with the morphological and histological changes of the lower ureter. In this study, we evaluate whether there is a correlation between the histological changes of the ureterovesical junction (UVJ) and the presence of scarring or loss of function as detected by renal scintigraphy.

2. Materials and methods

We retrospectively evaluated all pathological specimens of 18 cases who underwent ureteroneocystostomy (UNC) with the diagnosis of VUR or UVO between January 2008 and December 2011 at our clinic. The only inclusion criterion for the study was to have been operated on for UNC.

The decision for ureteroneocystostomy was made when an obstructive pattern together with decreased function was seen on renal scintigraphy in UVO cases and when there was grade 5 reflux in a child older than 1 year in VUR cases. Lower end specimens from the excised ureter were evaluated.

The total urinary specimens of UVO cases were processed for histopathological evaluation. To assess the number of nerve bundles the most representative block for obstruction was chosen and 10 HPFs for each block were evaluated. To compare the smooth muscle staining, one block from the distal ureter was chosen for each case. Two samples were randomly taken from the distal ureter for VUR cases. Immunohistochemical studies were done with S-100, smooth muscle alpha-actin, collagen type 3,

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and caspase. The S-100 stain was used to determine the number of nerve bundles. Smooth muscle alpha-actin expression was evaluated to assess the muscular structure. Collagen type 3 increase was evaluated with type 3 collagen stain. Caspase stain was used to measure the activity of caspase, the most important effector of programmed cell death, in the specimens. MAG3 scintigraphy was used for all patients for renal parenchyma function imaging.

Renal functions were compared using the histopathological evaluations of the ureter's lower end in both groups. SPSS 11.5 for Windows was used for analysis. Categorical variables were evaluated with Fisher's exact chi-square test.

3. Results

We retrospectively evaluated the pathological specimens of 18 subjects aged 1 month to 6 years (mean: 3.5 years) including 6 females and 12 males (Table 1). The 7 UVO patients, aged 5 months to 6 years (mean age: 38.5 months), included 1 (14.3%) female and 6 (85.7%) males and the left ureters were affected. The 11 VUR patients, aged 12 months to 12 years (mean age: 44.2 months), included 5 (45.5%) females and 6 (54.5%) males, with 4 (36.4%) cases of left-sided, 4 (36.4%) cases of right-sided, and 3 (27.2%) cases of bilateral involvement. The mean renal function on the affected side was 31.9% in the VUR group and 27.57% in the UVO group.

Mean staining values with the immunohistochemical nerve stain S-100 was 27.8 ± 8.54 (range: 15–42) in the VUR group and 14.0 ± 5.77 (range: 4–20) in the UVO group, and this difference was statistically significant ($P = 0.002$) (Figure 1). Smooth muscle alpha-actin expression was diffuse in VUR cases and variable in UVO cases with a statistically significant difference ($P < 0.001$).

Caspase activity was marked in four of seven UVO cases and six of eleven VUR cases. Similarly, staining with collagen type 3 was marked in three of seven UVO cases and five of eleven VUR cases. There was no statistically significant difference for caspase activity and type 3 collagen staining ($P > 0.05$). We found no statistically significant relationship between S-100, alpha-actin, type 3 collagen, and caspase stain levels ($P > 0.05$).

Alpha-actin expression in the distal ureter was variable in UVO cases and diffuse in VUR cases. This indicates that the smooth muscle structure is markedly defective in UVO cases when compared to VUR cases (Figure 2). The histopathological staining of the nerve bundle structure showed markedly decreased S-100 staining in UVO cases compared with VUR cases. We found that the distal ureter nerve bundle loss and the smooth muscle structure disturbance were more prominent in UVO than in VUR.

There was a statistically significant relationship between alpha-actin staining levels and renal function values in VUR cases ($P < 0.05$). The renal function was significantly better in VUR cases with normal actin levels compared to those with low levels (Table 2). There was no significant relationship between actin levels and renal function in UVO cases ($P > 0.05$). There was also

Table 1. The levels of S-100, actin, collagen, and caspase staining in VUR and UVO cases.

Patient characteristics	VUR (n = 11)		UVO (n = 7)		Total (n = 18)	
	Number	%	Number	%	Number	%
Sex						
Female	5	45.5	1	14.3	11	61.1
Male	6	54.5	6	85.7	7	38.9
S-100	P = 0.002					
Low	2	18.2	4	57.1	6	33.3
Normal	9	81.8	3	42.9	12	66.7
Actin	P < 0.001					
Low	1	9.1	5	71.4	6	33.3
Normal	10	90.9	2	28.6	12	66.7
Collagen	P > 0.05					
Low	5	45.5	3	42.9	8	44.4
Normal	6	54.5	4	57.1	10	55.6
Caspase	P > 0.05					
Low	6	54.5	4	57.1	10	55.6
Normal	5	45.5	3	42.9	8	44.4

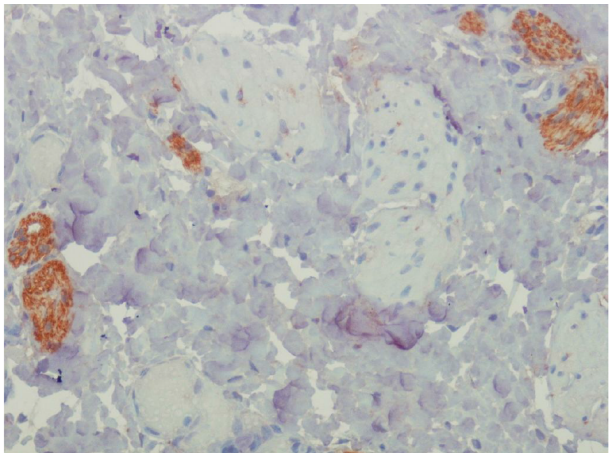

Figure 1. The nerve bundles of muscle tissue in a case of VUR (S-100, 100×).

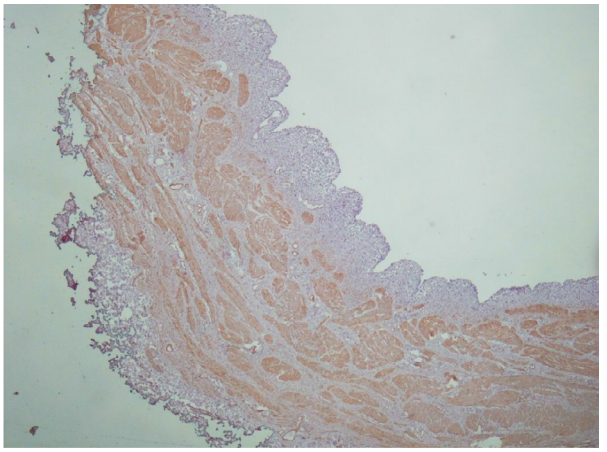

Figure 2. Actin expression in smooth muscle in a case of VUR (S-100, 100×).

no significant relationship between S-100, collagen, or caspase levels and renal function values in either VUR or UVO patients ($P > 0.05$).

4. Discussion

Structural disturbances of the UVJ lead to anomalies such as VUR or UVO (2–8). The exact role of histopathological anomalies in the emergence of UVO or VUR is not clear. A nerve innervation defect, muscle or extracellular matrix structural changes, or increased cellular apoptosis is thought to play a role in vesicoureteral junction disorders such as UVO and VUR (1–5,8).

It is now possible to determine a possible innervation defect with neuronal markers such as S-100 and muscle tissue pathology with smooth muscle alpha-actin expression using immunohistochemical techniques. Type 3 collagen staining is used to evaluate extracellular matrix changes while caspase stain is used to evaluate cellular apoptosis (4,5). We investigated the number of nerve bundles, smooth muscle alpha-actin expression, type 3 collagen ratio, and apoptosis increase in the pathology sections of the distal ureter in UVO and VUR cases. UVO cases showed inadequate nerve and muscle cells when compared to VUR cases. We found no difference between caspase activity showing increased apoptosis or extracellular matrix collagen type 3 accumulation that leads to ureter lower-end rigidity in VUR cases compared to UVO cases.

The marked disturbance in nerve bundle and smooth muscle structures in UVO cases compared to VUR cases seems to be an adjunctive sign explaining UVJ obstruction development (3–8). We think that the disturbance in muscle and nerve conduction in the ureter lower end explains the distal end stenosis. Its higher incidence in VUR cases compared to UVO cases indicates the need for evaluation of structural and functional disorders in the pathogenesis of VUR.

The renal function values in VUR cases with normal actin values were significantly higher than in those with low actin levels ($P < 0.05$). Marked renal function loss was seen in patients with a defective smooth muscle at the ureter's lower end. The muscle defect in the ureter distal end increased functional loss and scarring in the urinary system.

Histopathological evaluation of the UVJ can help to understand the etiopathogenesis of disorders. The relationship between the severity of UVJ and kidney damages can be demonstrated. Presence of severe renal damage may suggest that the anomaly of UVJ is more severe. Therefore, these findings may help in deciding about the timing of surgery.

In our study, we think that the major limitation is sample size. The study was retrospective. In a future study, the number can be increased, and it should be planned with a more homogeneous group.

In conclusion, we found that nerve and muscle cells were defective in UVO when compared to VUR, but

Table 2. Renal functions in VUR and UVO cases.

Renal function (%)	VUR (n = 11)	UVO (n = 7)
100–80	-	-
79–60	-	-
59–40	2	1
39–20	7	3
19–0	2	3

collagen 3 accumulation and cell apoptosis showed no difference when UVO and VUR, the two main pathologies of the UVJ, when compared. The decrease in muscle cells and nerve fibers contributes to explaining UVO while the lack of a difference in collagen type 3 and apoptosis values did not contribute to the explanation of ureter lower-end pathologies. Larger renal function defects in VUR cases with defective smooth muscle in the ureter's lower end indicate a relationship between ureter lower-end pathology and renal damage.

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