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Comparison of different pathological markers in predicting pyeloplasty outcomes in children☆,☆☆,★

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ABSTRACT

Purpose: To compare the efficacy of pathological markers like Interstitial cells of Cajal (ICC), neurons and Collagen to Muscle ratio (CM ratio), in predicting pyeloplasty outcomes.
Methods: Histological sections from 31 patients with UPJO were analyzed for ICC & neurons on immunohistochemistry and CM ratio on Masson's trichrome staining. Post-operative outcomes were analyzed at 1-year follow up; expressed as excellent, moderate or mild improvement, static and deterioration based on the three factors: ultrasound grade, differential renal function and renogram drainage pattern. The pathological findings were correlated with clinical outcomes.
Results: The study group (n = 31) had a mean age 2.9 (0.6) years (M: F = 22:9). UPJ segment had significantly less ICC/neurons and more collagen compared to normal ureter (p = 0.001). Pathological parameters at the anastomosed end of ureter had a better correlation than those at UPJ with clinical outcome. CM ratio with a stronger correlation (r = − 0.94; p = 0.001) was a better predictor of prognosis than ICC (r = 0.76; p = 0.01) or neuron (r = 0.83; p = 0.01) density. ICC > 10/HPF, neurons > 6/HPF and CM ratio < 1.2 at ureteric end anastomosed were predictors of success.
Conclusions: CM ratio analysis at anastomosed ureter is a superior marker for predicting pyeloplasty outcomes.
Level of Evidence: Type 2: Development of diagnostic criteria in a consecutive series of patients.

Ureteropelvic junction obstruction (UPJO) is the most common form of urinary tract obstruction in children [1] and the surgical correction typically involves a dismembered pyeloplasty. It is usually a successful procedure with failure rate of 5–7% [2,3]. An aperistaltic narrow segment has been proposed as a cause of UPJO in children [4,5]. While Stringer [6] claimed that there is no sound anatomical basis for existence of a region described as uretero pelvic junction (UPJ), Shafik and Sherif supported the existence of a muscular sphincter at UPJ. [7] Although the exact etiology of UPJO is still unknown, surgeons often send the excised narrow segment for routine histopathology [5,8] which typically reveals fibrosis and only inflammatory cell infiltrate.

Further detailed studies have shown that interstitial cells of Cajal (ICC) play an important role as a pacemaker in promoting peristaltic wave and pushing the bolus of urine down the ureter [9]. A decrease in ICC density at UPJO has been described as a factor in the etiology of hydronephrosis [10–16]. Decrease in neurons [5,17], smooth muscle disarray [18–21], increase in collagen and elastin content [1,13,22–24], have all been described in the etiology of UPJO. While most of the above studies have analyzed the UPJO segment from the diagnostic point of view, only two studies have studied the resected margin of the anastomosed end of ureter with prognostication in mind [25,26]. The aim of the present study is to compare the efficacy of pathological markers like ICC, neurons and Collagen to Muscle ratio (CM ratio), in prediction of prognosis after pyeloplasty.

1. Materials and methods

This was a prospective study performed between August 2017 and July 2018 after obtaining the necessary institutional ethics committee

Abbreviations: UPJ, Uretero pelvic junction; UPJO, Uretero pelvic junction obstruction; ICC, Interstitial cells of Cajal; CM ratio, Collagen to muscle ratio; US, Ultrasonogram; DRF, Differential renal function; APD, Antero posterior diameter of renal pelvis; SFU, Society of fetal urology grading of hydronephrosis; CD 117, Immunohistochemical marker for ICC; S 100, Immunohistochemical marker for neurons; HPF, High power field.

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approval ((IEC-NI/17/59/34)). Informed consent was obtained from all the patients and all procedures complied with the declaration of Helsinki.

1.1. Patient groups

The study group comprised of all consecutive patients who underwent open pyeloplasty for unilateral UPJO. Those with associated vesico ureteric reflux, posterior urethral valve, vesico ureteric junction obstruction and duplication were excluded. In addition those for whom a secondary/extrinsic cause of UPJO was a possibility (crossing vessel) were also excluded. Among 35 patients recruited, two were excluded for failure to follow-up and two for post-operative complications (1 urosepsis; 1 leak) that could confound the outcome leaving the remaining ($n = 31$) as the study group.

1.2. Treatment protocol

All patients were pre-operatively assessed with ultrasound (US), and diuretic renogram (Tc ^{99}MAG3) for differential renal function (DRF) and drainage pattern. The indications for surgery were deterioration in any two of the above three parameters during the follow-up. Functional deterioration (10% drop in DRF) was seen in 23 patients while in 8 patients there was worsening of US along with the drainage pattern prompting the intervention. Open dismembered pyeloplasty was performed by the same surgeon (RB) in all cases. The UPJ segment was defined as the portion that lies between the pelvis and the point where the ureter width becomes normal (comparable to the distal ureter). The narrow segment was marked as UPJO and the resected lower end of the specimen was marked separately as the anastomosed ureteric end. Pyeloplasty was performed with interrupted 6–0 polyglactin sutures and a double-J-stent was kept for a period of 4–6 weeks.

1.3. Pathological analysis

1.3.1. Interstitial cells of Cajal

Immunohistochemical study using c-kit (CD117) for ICC was performed on formalin-fixed and paraffin-embedded tissue samples using EP10 mono-clonal antibody of rabbit for CD117 (BioGenex, 49,026, Milmont Drive, Fremont, CA94538). Positive controls were stained along with the cases, the known control for CD117 being gastro intestinal stromal tumor. ICC were spindle-shaped cells with stellate cytoplasmic extensions at both poles. Number of ICC/10 high power field (HPF) was assessed by an independent researcher, blinded to outcomes.

1.3.2. Neurons

Immunohistochemical study for evaluation of neurons was performed using 15E2E2 monoclonal antibody of mouse for S100, (BioGenex, 49,026, Milmont Drive, Fremont, CA94538). Positive controls were stained along with the cases, the known control for S 100 being neurofibroma. Number of neurons which stain dark with S 100 antibody /10HPF was assessed by an independent researcher (blinded to outcomes).

1.3.3. Masson's trichrome staining

Formalin-fixed and paraffin-embedded tissue samples were horizontally sectioned at 4 μm to examine muscle and collagen. Sections were stained using conventional Masson's trichrome, which highlights the extracellular matrix or collagen as blue and smooth muscle as red.

1.3.4. Collagen muscle ratio analysis

Quantitative estimate of collagen versus muscle content was performed by an independent observer using color image analysis described by Kim [27]. Digital photographs of Masson's Trichrome stained specimens were cropped to select area of interest excluding epithelium or adventitia. Color image analysis was performed using commercially available online color extraction tool powered by multicolor engine (Tiny Eye labs, Copyright © 2017 Idée Inc., 223 Queen St. E., Toronto, ON, Canada M5A 1S2). The areas corresponding to blue color were matched as collagen, with areas of red as muscle. The ratio of blue area to red area was considered as collagen to muscle ratio (CM ratio).

1.4. Surgical outcomes

All the patients were followed up at 3 monthly intervals with US and final post-operative outcome was analyzed at 1-year follow up based on the three factors: US grade, DRF and renogram drainage pattern (Table 1). Improvement by 1–2 points in all three parameters was expressed as excellent, in two parameters as moderate and in one parameter as mild improvement. Improvement/ deterioration was scaled based on hydronephrosis severity score (Table 1) described earlier [28]. Patients who remained unchanged on all three parameters were considered static. If deterioration in more than one parameter was noted at 1-year follow-up they were considered as failure and booked for a repeat pyeloplasty.

1.5. Statistical analysis

Data like ICC/10 HPF, neurons/ 10HPF and CM ratio were expressed as mean and median and were compared using Mann Whitney U test. Post-operative outcomes were compared with ICC, neurons and CM ratio with Pearson correlation. Outcomes from deterioration to excellent improvement were scaled 1 to 5 and linear regression analysis was performed to identify the number of ICC/ neurons and CM ratio required for a successful outcome. Data were analyzed using Statistical Package for Social Sciences, version 12.0 (SPSS, Chicago, IL, USA). A probability of <0.05 was considered significant.

2. Results

2.1. Clinical outcomes

The study group ($n = 31$) had a mean (s.d.) age of 2.9 (0.6) years ranging from 0.2–11 years (M: F = 22:9) the majority being prenatally diagnosed hydronephrosis. The median follow up was 16 months (range 12–19 months). Fig. 1 describes the outcomes. There was excellent improvement in 7 patients, moderate improvement in 16 and mild improvement in 3 patients. In 3 patients the outcome was static and they are still under follow-up. There was worsening in 2 (6%) patients at 1 year-follow up and both underwent a repeat pyeloplasty.

2.2. Pathological outcomes

Fig. 1 compares the distribution of pathological markers at the UPJ and anastomosed end of the ureter. The mean number of ICC/10 HPF was significantly lower ($p = 0.001$) at 5.3 (2.3) in UPJ compared to 12.4 (5.1) in the anastomosed end of ureter. The mean number of neurons/10 HPF was significantly lower ($p = 0.007$) at 5.1 (3.7) in UPJ compared 8.5 (3.8) in the anastomosed end of ureter. Mean CM ratio was significantly higher ($p = 0.001$) at 2.2 (0.72) in UPJ compared to 0.95 (0.48) in the ureter end used for anastomosis. Fig. 2 depicts representative examples of the pathological markers between UPJ and anastomosed end of the ureter. Specimens of anastomosed end of ureter had significantly higher ICC/ neurons compared to the UPJ. Specimens of UPJ had significantly higher collagen (blue areas) while the anastomosed end of ureter had higher smooth muscle (red areas). UPJ segment of the two patients (failures), who had repeat pyeloplasty, had high CM ratio and fibrosis.

Fig. 3 depicts the correlation between pathological parameters at UPJ and anastomosed end of ureter with the clinical outcome. Pathological parameters at the anastomosed end of ureter had a better correlation

Table 1
Clinical outcomes – and quantitative analysis of pathological markers in relation to clinical outcome.

Hydronephrosis severity score						
A. DRF (renogram)	B. Drainage pattern (renogram)			C. SFU grading/ APD (ultrasonogram)		
0 ≥ 45%	0 good drainage starts even before frusemide			0 normal (APD ≤ 5 mm)		
1 40–44%	1 good drainage starts only after frusemide			1 mild dilatation of pelvis (APD 6–9 mm)		
2 35–39%	2 delayed drainage after frusemide (equivocal)			2 moderate pelvis dilatation (APD 10–19 mm)		
3 30–34%	3 poor response to frusemide (plateau) + partial clearance in 2-h			3 pelvis & calyces dilated (APD 20–29 mm)		
4 < 30%	4 no response to frusemide (up-raising curve) + stasis in 2-h			4 severe pelvi calyeal dilatation + cortical thinning (APD ≥ 30 mm)		
(HSS) = A + B + C; Maximum score 12; Minimum score 0						
Post-operative outcomes				**Pathological parameters (mean) at anastomosed end of ureter**		
Clinical outcome	Parameters (DRF, drainage curve, USG)	Post op HSS - Pre op HSS	n = 31	ICC	Neurons	CM Ratio
Excellent Improvement	All three parameters improve by 1–2	5–6	7	18.2	14	0.3
Good improvement	Two parameters improve by 1–2	3–4	16	15.6	11.2	0.6
Mild improvement	One parameter improves by 1–2	1–2	3	13.4	9.1	0.8
No improvement	No parameter changes	0	3	9.4	5.3	1.2
Deterioration	Deterioration in one or more parameters	−1 or less	2	1.5	2.5	2.2

Hydronephrosis severity score (HSS) is based on three parameters, differential renal function (DRF), drainage pattern and ultrasound grade/anteroposterior diameter (APD) each scaled from 0 to 4.

with clinical outcome than those at UPJ. CM ratio showed a stronger correlation ($r = -0.94$; $p = 0.001$) and so was a better predictor of prognosis than ICC ($r = 0.76$; $p = 0.01$) or neuron ($r = 0.83$; $p = 0.01$). The predictors for success determined by linear regression analysis (Fig. 3) were: ICC of ≥10/HPF (95% CI 6–15), neurons ≥6/HPF (95% CI 3–23), and a CM ratio ≤ 1.2 (95% CI 1.9–0.7).

3. Discussion

While pyeloplasty is generally a successful surgery [1,25] on 5–7% occasions it fails [2,3]. While some authors have found little evidence to support a histological basis for pyeloplasty outcomes [16,26], others have identified presence of abnormalities in ICC, neurons and collagen-muscle matrix at UPJ [1–15,16,19–29]. Several of these histological markers like ICC, neurons and CM ratio have been reported to be of prognostic significance. In the present study we have compared the efficacy of pathological markers and proposed cut off ranges that may predict successful outcome.

Yang [12] compared the expression of ICC in histological specimens from UPJ segments between patients and controls. They reported that a reduction in ICC density may play an important role in the pathogenesis of UPJO. In the study done by Senol [15] ICC in the UPJ were graded as rare (0–3 cells/10 HPF), few (4–6 cells/10 HPF), and many (=7 cells/HPFs). Nearly 68% of cases in their study were graded as rare and this was similar to that reported by Inugala [25] in which 52% of cases were graded as negative. The study by Alper Eken [14] used a similar grading system and concluded that in UPJO, there was a decrease in the number of ICC, as well as the changes in the morphologic structure of the ICC, indicating their role as a pacemaker system in ureteral peristalsis. Apoznanski reported no distributional difference in c-kit-positive ICC between obstructed and unobstructed UPJ [16]. While most of the studies have focused on the UPJ segment, it is essential to study the resected end of distal ureter as the normality at the ureter used for anastomosis is far more crucial for the outcome [25].

Kim [27] studied CM ratio by color image analysis and found that it was an essential parameter in predicting recovery after pyeloplasty. They reported a mean CM ratio of 1.32 ± 0.79 in UPJ while only 0.30 ± 0.10 in normal controls. They felt that those with lower CM ratio, were associated with better postoperative improvement of hydronephrosis. They divided the patients according to the CM ratio into group one: ratio ≤1, group two: ratio 1–1.5 and group three: ratio >1.5 and found that the outcome was better in group one. However their findings [27] did not show a strong correlation [$r = -0.43$] as they only assessed the prognostic value of UPJ segment with clinical improvement. Issi [26] compared the histological markers at UPJ between successful and unsuccessful groups following pyeloplasty and reported no significant difference between collagen, elastin, fibrosis or ICC between the groups. While some authors [26,29] have failed to show the

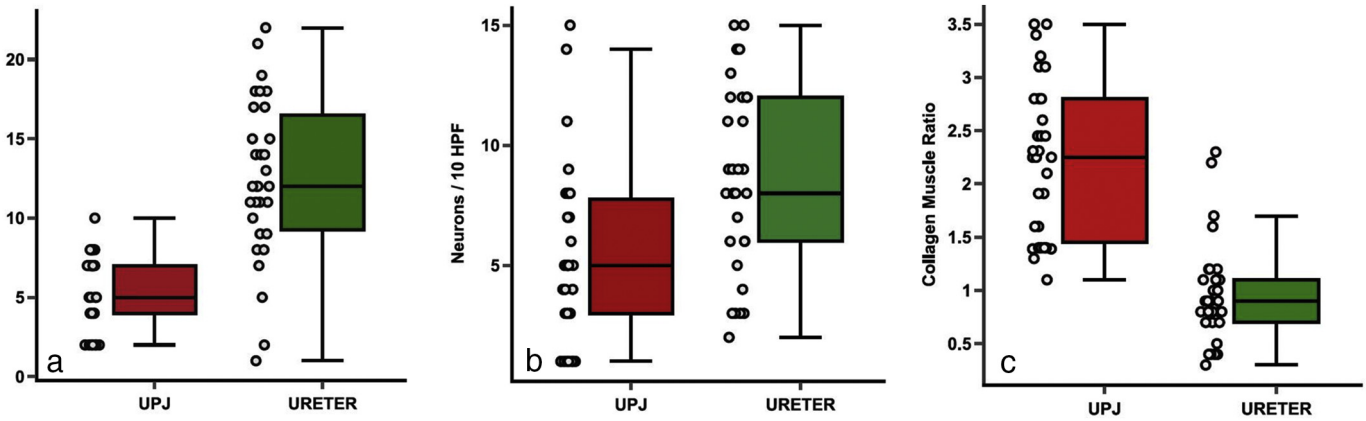

Fig. 1. Box cum scatter plot representing the differences in pathological parameters between UPJ and anastomosed end of ureter. Box plots represent median and quartiles while scatter plots represent actual values. Red boxes correspond to UPJ while green boxes anastomosed end of ureter. UPJ had significantly less ICC or neurons compared to anastomosed end of ureter. The CM ratio was significantly higher at UPJ compared to the anastomosed end of ureter.

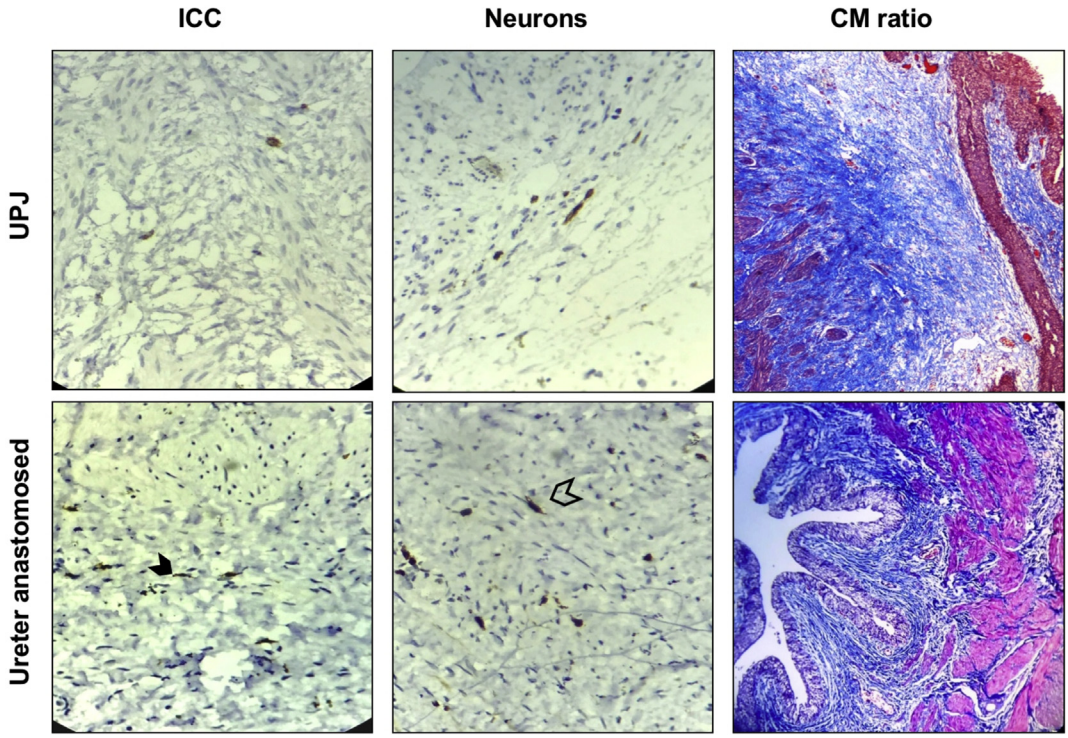

Fig. 2. Pathological parameters at UPJ versus anastomosed ureter Specimens of anastomosed end of ureter had significantly higher ICC (block arrow) or neurons (hollow arrow) compared to the UPJ. Specimens of UPJ had significantly higher collagen (blue areas) while the anastomosed end of ureter had higher smooth muscle (red areas).

association between pathological markers and outcome and felt that surgical technique is more important, we feel that they have missed the association because they only studied the UPJ segment itself.

The present study has shown that parameters at the anastomosed end of ureter correlate better with pyeloplasty outcomes than those at UPJO segment. ICC of ≥10/HPF, neurons ≥6/HPF, and a CM ratio ≤1.2 were identified as predictors for success in the present study. CM ratio at the anastomosed end of ureter was a better predictor of pyeloplasty outcomes than ICC or neurons. Sending the UPJ specimen for routine histopathology is of no use, as it demonstrates only fibrosis and inflammatory infiltrate. On the other hand, if the anastomosed end of ureter is marked and sent for CM ratio, we get a good prognostic tool to help clinician predict outcome.

While immuno-histochemistry for ICC and neurons may not be widely available or affordable, Masson's trichrome staining is commonly used and CM ratio analysis should be feasible widely. The authors favor sending the anastomosed end of the ureter for CM ratio analysis for prognostication. The findings of this study could also help in planning a closer follow up for those with unsatisfactory pathological findings at the anastomosed end of ureter. Keeping the stent longer in this group may be an option to prevent recurrence. The pitfalls of our study are small numbers. Although we feel exclusion of cases with lower polar vessels was appropriate, some might consider this as a selection bias. Further research should focus on development of intra operative markers that could help in identifying normal ureter by frozen section/ special stain during pyeloplasty. Further larger studies with cost benefit analysis are warranted to study the role of pathological markers in predicting pyeloplasty outcomes.

4. Conclusions

Pathological markers at the anastomosed end of ureter correlate better with clinical outcomes than those at UPJ. Sending the resected end of

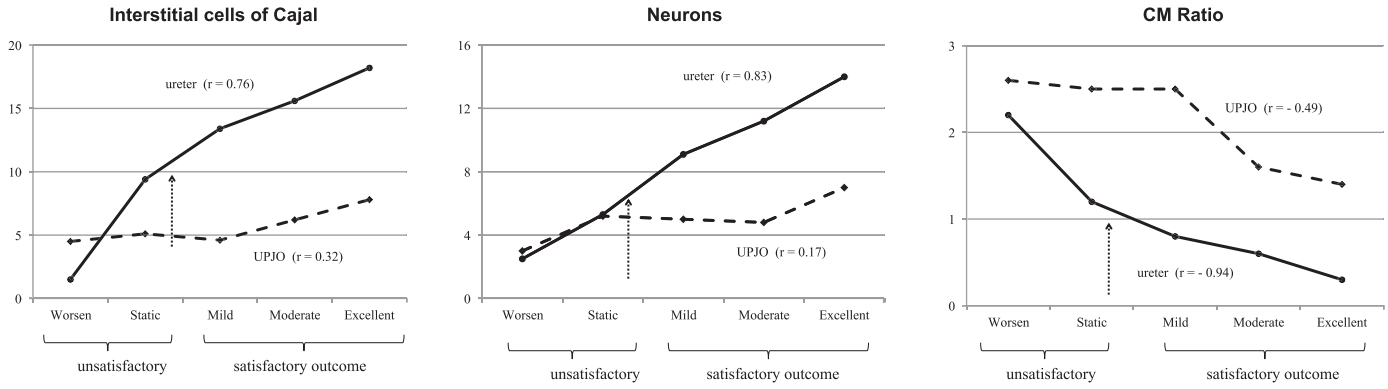

Fig. 3. Correlation between pathological parameters at UPJO/ anastomosed end of ureter with clinical outcome Pathological parameters at the anastomosed end of ureter (solid line) had better correlation with clinical outcome than those at UPJ (dashed line). CM ratio at the resected end of ureter with a strongest correlation ($r = -0.94$; $p = 0.001$) was the best predictor of pyeloplasty outcomes. Dotted arrow points to predictors for success determined by regression analysis: ICC of ≥10/HPF, neurons ≥6/HPF, and a CM ratio ≤1.2.

the ureter for collagen to muscle ratio analysis gives the best possible prognostic prediction on pyeloplasty outcomes.

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IRB approval

IEC-NI/17/APR/59/34.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Declaration of competing interest

None to declare.

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References

[1] Yoon JY, Kim JC, Hwang TK, et al. Collagen studies for pediatric ureteropelvic junction obstruction. Urology. 1998;52:494–7 discussion 497-8 . https://doi.org/10.4274/jus.1655.
[2] Romao RLP, Koyle MA, Pippi Salle JL, et al. Failed pyeloplasty in children: revisiting the unknown. Urology. 2013;82:1145–7. https://doi.org/10.1016/j.urology.2013.06.049.
[3] Thomas JC, DeMarco RT, Donohoe JM, et al. Management of the failed pyeloplasty: a contemporary review. J Urol. 2005;174:2363–6. https://doi.org/10.1097/01.ju.0000180420.11915.31.
[4] Tsuji Y, Kinukawa T, Suzuki A, et al. Identification of the narrow lumen of the ureter using a Fogarty catheter during laparoscopic pyeloplasty. Int J Urol. 2013;20:445–7. https://doi.org/10.1111/j.1442-2042.2012.03154.x.
[5] Harish J, Joshi K, Rao KLN, et al. Pelviureteric junction obstruction: how much is the extent of the upper ureter with defective innervation needing resection? J Pediatr Surg. 2003;38:1194–8. http://www.ncbi.nlm.nih.gov/pubmed/12891491.
[6] Stringer MD, Yassaie S. Is the pelviureteric junction an anatomical entity? J Pediatr Urol. 2013;9:123–8. https://doi.org/10.1016/j.jpurol.2011.08.009.
[7] Shafik A, Al-Sherif A. Ureteropelvic junction: a study of its anatomical structure and function. Ureteropelvic junction sphincter? Eur Urol. 1999;36:150–6; discussion 156-7. https://doi.org/10.1159/000067987.
[8] Mut T, Acar Ö, Oktar T, et al. Intraoperative inspection of the ureteropelvic junction during pyeloplasty is not sufficient to distinguish between extrinsic and intrinsic causes of obstruction: correlation with histological analysis. J Pediatr Urol. 2016;12:223.e1–6. https://doi.org/10.1016/j.jpurol.2016.02.016.
[9] Di Benedetto A, Arena S, Nicotina PA, et al. Pacemakers in the upper urinary tract. NeurourolUrodyn. 2013;32:349–53. https://doi.org/10.1002/nau.22310.
[10] Solari V, Piotrowska AP, Puri P. Altered expression of interstitial cells of Cajal in congenital ureteropelvic junction obstruction. J Urol. 2003;170:2420–2. https://doi.org/10.1097/01.ju.0000097401.03293.f0.
[11] Kuvel M, Canguven O, Murtazaoglu M, et al. Distribution of Cajal like cells and innervation in intrinsic ureteropelvic junction obstruction. Arch Ital Di Urol Androl Organo Uff [Di] Soc Ital Di Ecogr Urol e Nefrol. 2011;83:128–32. http://www.ncbi.nlm.nih.gov/pubmed/22184836.
[12] Yang X, Zhang Y, Hu J. The expression of Cajal cells at the obstruction site of congenital pelviureteric junction obstruction and quantitative image analysis. J Pediatr Surg. 2009;44:2339–42. https://doi.org/10.1016/j.jpedsurg.2009.07.061.
[13] Mehrazma M, Tanzifi P, Rakhshani N. Changes in structure, interstitial Cajal-like cells and apoptosis of smooth muscle cells in congenital ureteropelvic junction obstruction. Iran J Pediatr. 2014;24:105–10. http://www.ncbi.nlm.nih.gov/pubmed/25793054.
[14] A. Eken, S. Erdogan, Y. Kuyucu, G. Seydaoglu, S. Polat, N. Satar, Immunohistochemical and electron microscopic examination of Cajal cells in ureteropelvic junction obstruction., Can Urol Assoc J 7 (n.d.) E311–6. doi:. https://doi.org/10.5489/cuaj.11293.
[15] Senol C, Onaran M, Gurocak S, et al. Changes in Cajal cell density in ureteropelvic junction obstruction in children. J Pediatr Urol. 2016;12:89.e1–5. https://doi.org/10.1016/j.jpurol.2015.08.010.
[16] Apoznanski W, Koleda P, Wozniak Z, et al. The distribution of interstitial cells of Cajal in congenital ureteropelvic junction obstruction. Int Urol Nephrol. 2013;45:607–12. https://doi.org/10.1007/s11255-013-0454-7.
[17] Kaya C, Bogaert G, de Ridder D, et al. Extracellular matrix degradation and reduced neural density in children with intrinsic ureteropelvic junction obstruction. Urology. 2010;76:185–9. https://doi.org/10.1016/j.urology.2009.09.097.
[18] Hosgor M, Karaca I, Ulukus C, et al. Structural changes of smooth muscle in congenital ureteropelvic junction obstruction. J Pediatr Surg. 2005;40:1632–6. https://doi.org/10.1016/j.jpedsurg.2005.06.025.
[19] Kajbafzadeh A-M, Payabvash S, Salmasi AH, et al. Smooth muscle cell apoptosis and defective neural development in congenital ureteropelvic junction obstruction. J Urol. 2006;176:718–23 discussion 723 . https://doi.org/10.1016/j.juro.2006.03.041.
[20] Gosling JA, Dixon JS. Functional obstruction of the ureter and renal pelvis. A histological and electron microscopic study. Br J Urol. 1978;50:145–52. http://www.ncbi.nlm.nih.gov/pubmed/753449.
[21] Notley RG. The structural basis for normal and abnormal ureteric motility. The innervation and musculature of the human ureter. Ann R Coll Surg Engl. 1971;49:250–67. http://www.ncbi.nlm.nih.gov/pubmed/4940038.
[22] Kim DS, Noh JY, Jeong HJ, et al. Elastin content of the renal pelvis and ureter determines post-pyeloplasty recovery. J Urol. 2005;173:962–6. http://www.ncbi.nlm.nih.gov/pubmed/15711350.
[23] Murakumo M, Nonomura K, Yamashita T, et al. Structural changes of collagen components and diminution of nerves in congenital ureteropelvic junction obstruction. J Urol. 1997;157:1963–8. http://www.ncbi.nlm.nih.gov/pubmed/9112572.
[24] S.K. Özel, H. Emir, S. Dervişoğlu, N. Akpolat, B. Şenel, A. Kazez, Y. Söylet, G. Çetin, N. Danişmend, S.N.C. Büyükünal, The roles of extracellular matrix proteins, apoptosis and c-kit positive cells in the pathogenesis of ureteropelvic junction obstruction., J Pediatr Urol. 6 (2010) 125–9. doi:. https://doi.org/10.1016/j.jpurol.2009.07.011.
[25] A. Inugala, R.K. Reddy, B.N. Rao, S.P. Reddy, R. Othuluru, L. Kanniyan, N. Kumbha, S. Srirampur, Immunohistochemistry in Ureteropelvic junction obstruction and its correlation to postoperative outcome., J Indian Assoc Pediatr Surg 22 (n.d.) 129–133. doi:. https://doi.org/10.4103/jiaps.JIAPS_254_16.
[26] Issi O, Deliktas H, Gedik A, et al. Does the histopathologic pattern of the ureteropelvic junction affect the outcome of pyeloplasty. Urol J. 2015;12:2028–31. http://www.ncbi.nlm.nih.gov/pubmed/25703913.
[27] Kim WJ, Yun SJ, Lee TS, et al. Collagen-to-smooth muscle ratio helps prediction of prognosis after pyeloplasty. J Urol. 2000;163:1271–5. http://www.ncbi.nlm.nih.gov/pubmed/10737527.
[28] Babu R, Venkatachalapathy E, Sai V. Hydronephrosis severity score: an objective assessment of hydronephrosis severity in children-a preliminary report. J Pediatr Urol. 2019;15:68.e1–6. https://doi.org/10.1016/j.jpurol.2018.09.020.
[29] Koleda P, Apoznanski W, Wozniak Z, et al. Changes in interstitial cell of Cajal-like cells density in congenital ureteropelvic junction obstruction. Int Urol Nephrol. 2012;44:7–12. https://doi.org/10.1007/s11255-011-9970-5.