Original Article

Association between Intraoperative Anatomical Variation and Histopathological Parameters in Cases of Ureteropelvic Junction Obstruction in Children: A Cross-Sectional Study

Shailesh Solanki, Prema Menon, Manasa Reddy, Mayur Parkhi[1], Kirti Gupta[1], Pramod K Gupta[2], Nitin James Peters, Ram Samujh

Departments of Pediatric Surgery, [1]Histopathology and [2]Biostatistics, PGIMER, Chandigarh, India

Abstract

Introduction: The intraoperative anatomical findings (IOAF) of all ureteropelvic junction obstruction (UPJO) cases are not identical. Moreover, there is also controversy in the literature regarding histopathological (HP) findings in cases of UPJO. In the present study, we evaluated different IOAF and assessed their association with specific HP parameters. **Materials and Methods:** This was a cross-sectional study set-up, which was carried out in a tertiary care centre. Children with UPJO who underwent surgery between 2017 and 2020 were enrolled. The following IOAF were noted: Type of pelvis (extrarenal or intrarenal), insertion of the ureter (high or normal), presence of lower pole crossing vessel (CV), negotiation of UPJ segment with double J stent (3 Fr) and length of internal narrowing (LIN) at UPJ. The resected segment of UPJ was assessed at three levels (pelvis, UPJ and ureter) for various HP parameters including fibrosis, oedema, inflammation and smooth muscle hypertrophy (SMH). **Results:** Thirty-nine children were included in the study with a mean age of 31 months. The summary statistics of IOAF were intrarenal pelvis in 5 cases, high insertion of the ureter (HIU) in 9, CV in 6, negotiable UPJ in 23, and 16 cases showed LIN >1 cm. All cases showed SMH at the pelvis region and SMH with fibrosis at the UPJ region. At the pelvis region, there was an association between (1) HIU with oedema and chronic inflammation (CIF), (2) CV with CIF and (3) LIN with CIF and SMH. At the UPJ region, there was an association between (1) CV and negotiable UPJ with less fibrosis and (2) LIN with SMH. At the ureteric end, CV showed an association with less fibrosis and more CIF. **Conclusion:** All UPJO cases have some common HP findings. Although, some particular IOAF, i.e., presence of CV, negotiable UPJ, HIU and LIN showed association with specific HP parameters.

Keywords: Crossing vessel, high insertion of the ureter, histopathology, intraoperative anatomy, pelvic ureteric junction obstruction, ureteropelvic junction obstruction

Introduction

Ureteropelvic junction obstruction (UPJO) is an abnormality that can present at any age and can have varied presentations including antenatal diagnosis, abdominal pain, lump or recurrent urinary tract infection. Two separate aetiologies have been used to describe UPJO, i.e., intrinsic and extrinsic. The intrinsic disease represents an aperistaltic or stenotic segment of the ureter while extrinsic causes include lower pole crossing vessel (CV).[1] During surgery of UPJO, the intraoperative anatomical findings (IOAF) are not identical, neither for intrinsic nor for extrinsic pathology.

In the literature, there is no consensus whether it is the same pathogenesis in all UPJO, across all ages and different types of presentation.[1-3] The various theories proposed as the cause of UPJO include an increase in the collagen between the muscle bundles and elastin in the adventitia, abnormal muscle orientation, infolding of ureteral mucosa, CV and a combined neurogenic-myogenic theory for congenital UPJ obstruction.[4,5]

As the pathophysiology is still unclear, the goal of this study was to determine any association between varied IOAF with different HP parameters. This is the first study which considers

Address for correspondence: Dr. Shailesh Solanki, Block 5d, Room No. 5422, Advanced Pediatric Centre, PGIMER, Sector 12, Chandigarh - 160 012, India.
E-mail: drshaileshpgi@gmail.com

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different intraoperative factors during histopathological (HP) evaluation.

Materials and Methods

This was a cross-sectional study setup that was conducted in the department of paediatric surgery at a tertiary care centre after approval by the Institutional Ethics Committee. All children with <12 years of age with UPJO who underwent pyeloplasty between 2017 and 2020 were enrolled in the study. Patients with redo pyeloplasty, vesicoureteric reflux, vesicoureteric junction obstruction and history of pyonephrosis were excluded.

All children underwent standard investigation protocol as well as operative procedure. For the confirmation of diagnosis, ultrasound, L-ethylenedicysteine nuclear scan and intravenous pyelography was done pre-operatively. The decision of surgery was taken after considering multiple factors includes presentation, symptoms, drainage pattern on the scan, kidney function as well as trends of different renal parameters during follow-up. All children underwent standard extraperitoneal Anderson-Hynes open pyeloplasty. The following intraoperative findings were noted: Type of pelvis (extrarenal or intrarenal), insertion of the ureter (high or normal), presence of lower pole CV, negotiation of UPJ segment with double J stent (3 Fr) and length of internal narrowing (LIN) at UPJ. The resected UPJ segment was sent for HP examination and it consisted of the pelvis above, narrow UPJ in middle and ureter below, as shown in Figure 1. The three regions were marked with different colour sutures and all HP parameters evaluations were done on these three different regions.

Histopathological assessment

All excised UPJ segment specimens were kept in 10% (weight/volume) phosphate-buffered formalin for 24–48 h. The suture-oriented specimens were grossed and sections from three representative areas (pelvis above, UPJ and ureter) were processed as per the standard protocol. A 5 µm-thick section of formalin-fixed paraffin-embedded tissue blocks were prepared for haematoxylin and eosin staining. All the stained slides were assessed by the two expert histopathologists who were blinded for the intraoperative details. The assessment of the HP parameters was based on the status of the lamina propria, and the muscularis propria that were graded as follows:[1]

1. In the lamina propria, the presence of fibrosis (0 = none, 1+ = limited to the lamina propria, 2+ = involving the muscularis propria and 3+ = replacing the muscularis propria and extending into the adventitial layer), oedema (present or absent) and inflammation (including acute and chronic; each divided into mild, moderate and severe) were evaluated
2. In the smooth muscle layer, the presence of hypertrophy was assessed as absent, mild, moderate and severe wherein the thickness of the muscularis propria was compared with that of lamina propria.

Statistical analysis

The summary statistics for qualitative variables were reported by frequencies whereas quantitative variables were with mean and standard deviation given the variable holds normality. The significance of the association between intraoperative anatomical variation and HP variables was tested using the Chi-squared test. Henceforth, the Cramer's V-test was also used, which is a post-test of Chi-squared test, tells the association is little, close to zero, and strong, close to one. All aforementioned tests were performed at 5% level of significance. The analysis was performed using statistical software R-GUI (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria URL https://www.R-project.org/) version 3.6.1 on a 64-bit machine with the Windows 10 operating system.

Results

Forty-nine patients were enrolled in the study. Thirty-nine patients fulfilled the inclusion criteria, whereas 10 patients were excluded because of the following: A history of

Table 1: Epidemiological characteristics and intraoperative findings

Parameters	Subgroup	Number of children in subgroup
Age	<1 year/>1 year	17/22
Sex	Male/female	30/9
Clinical presentation	AD/pain/lump	18/14/7
Type of pelvis	Extrarenal pelvis/ intrarenal pelvis	34/5
UPJ patency	Negotiable UPJ/ nonnegotiable UPJ	23/16
Insertion of ureter	NIU/HIU	30/9
LIN at UPJ	<1 cm/>1 cm	23/16
Presence of CV	Absent/present	33/6

AD: Antenatally diagnosed, CV: Crossing vessel, LIN: Length of internal narrowing, HIU: High insertion of ureter, NIU: Normal insertion of ureter, UPJ: Uretero-pelvic junction, >1 year: More than 1 year old, <1 year=Less than 1 year old, <1 cm: Less than one centimeter, >1 cm: More than one centimeter

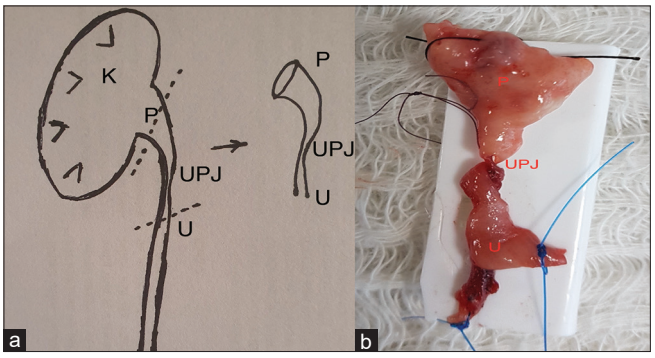


Figure 1: (a) Showing schematic line diagram of usual anatomy and excised specimen of UPJ region (b) Resected specimen with fixation and markings. K: Kidney, U: Ureter, P: Pelvis, UPJ: Uretero-pelvic junction

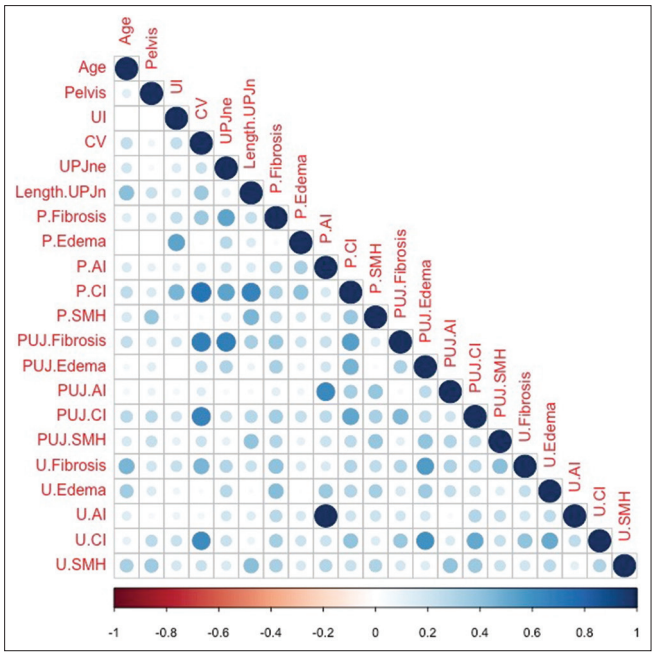


Figure 2: The graph represents strength of association between individual intraoperative finding and particular histopathological parameters are displayed together based on Cramer's V statistics. Pelvis: Type of pelvis i.e., intrarenal or extrarenal, UI: Type of ureteric insertion i.e., high or normal, CV: Crossing vessel, UP Jne: Ureteropelvic junction negotiable or nonnegotiable, Length UP Jn: Length of internal narrowing at uretro-pelvic junction, P: Pelvic, AI: Acute inflammation, CI: Chronic inflammation, SMH: Smooth muscle hypertrophy, PUJ: Pelvi ureteric junction, U: Ureteric

pyonephrosis (7), redo-pyeloplasty (2) and associated VUR (1). The mean age was 31 months while the median age at the time of surgery was 3 years. The epidemiological parameters, clinical presentation and intraoperative findings are as mentioned in Table 1. The frequency of HP parameters and intraoperative findings at a different location is summarized in Table 2. The result of statistical analysis was summarized by Cramer's V-test as reported by Figure 2.

All cases showed smooth muscle hypertrophy (SMH) at the pelvis region while at the UPJ region along with SMH, fibrosis was also present [Figure 3]. There was no single case that showed moderate or severe acute inflammation at the UPJ area or ureteric region. At the pelvis region, there was a statistically significant positive association [Figure 2] between (1) HIU with oedema and chronic inflammation (CIF) (2) CV with CIF (3) LIN with CIF and SMH. At the UPJ region, there was a statistically significant negative association between (1) CV with fibrosis (2) Negotiable UPJ with fibrosis; and positive association with more LIN with SMH. At the ureteric end, there was a significant association between the presence of CV with less fibrosis and more CIF.

Discussion

The UPJ obstruction (UPJO) is the most important cause of antenatal hydronephrosis which is one of the most common congenital anomalies of the genitourinary tract.

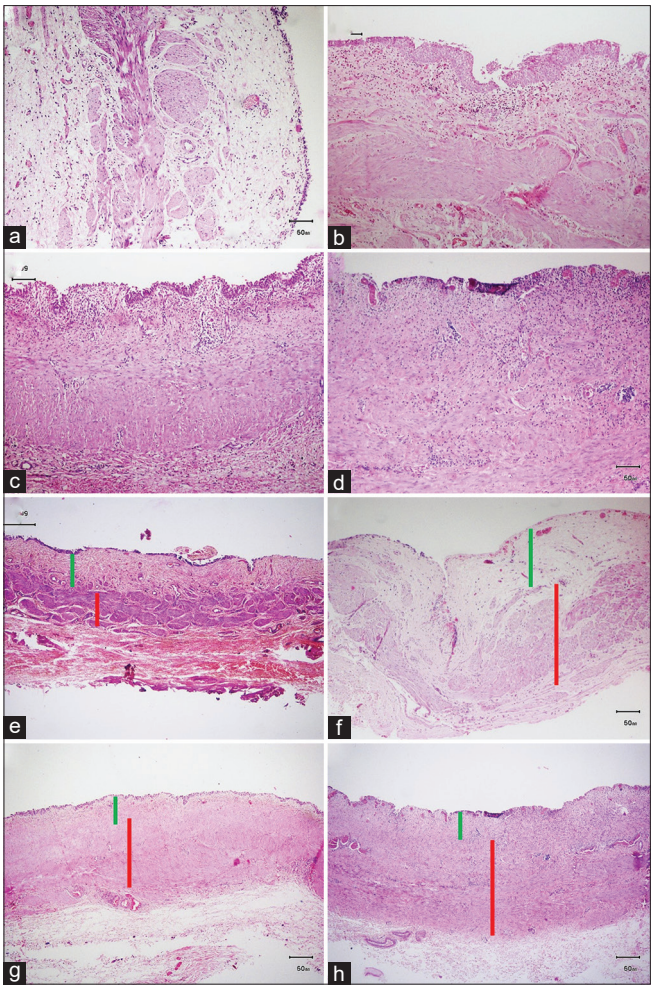


Figure 3: The morphological changes seen in uretero-pelvic obstruction cases includes: (a) edema, (b) mild inflammation, (c) moderate inflammation, and (d) severe inflammation. The thickness of muscularis propria (red vertical line) in comparison to that of lamina propria (green vertical line) can be appreciated in the respective images. (e) Normal thickness. (f) Mild hypertrophy. (g) Moderate hypertrophy. (h) Severe hypertrophy. The smooth muscle hypertrophy is accompanied by fibrosis involving lamina propria as well as muscularis propria (f-h) (H and E, a-d: ×200, e-h: ×40)

The UPJO is considered mechanical as well as functional obstruction.

The normal histology of UPJ consists of 3 layers – mucosa, muscularis and adventitia. The muscularis is thin and consists of muscle cells, interspersed by connective tissue. The inner muscle layer is circular and the outer consists of longitudinal muscle.

There are several studies in the literature which mention the HP examination in cases of UPJO with intrinsic obstruction and with CV pathology as well as compared it with normal UPJ histopathology.[1,2,6-8] The result of some studies supports each other while others contradict. We analysed those studies and found that, there were certain confounding factors in the reported studies which might be the reason for the discrepancy

Table 2: Frequency of histopathological parameters at pelvis/ureteropelvic junction/ureter respectively and its association with intraoperative findings

HP parameters at pelvis/UPJ/ureter	Intra operative findings									
	ER pelvis	IR pelvis	UPJ negotiable	UPJ nonnegotiable	CV-present	CV-absent	NIU	HIU	LIN <1 cm	LIN >1 cm
Fibrosis-none	2/0/2	0/0/0	2/0/2	0/0/0	0/0/0	2/0/2	1/0/1	1/0/1	1/0/2	1/0/0
Fibrosis-mild	19/10/15	4/1/3	15/9/12	8/2/6	6/6/6	17/5/12	17/7/15	6/4/3	15/9/11	8/2/7
Fibrosis-moderate	9/9/15	1/3/2	2/11/8	8/1/9	0/0/0	10/12/17	8/10/13	2/2/4	4/7/9	6/5/8
Fibrosis-severe	4/15/2	0/1/0	4/3/1	0/13/1	0/0/0	4/16/2	4/13/1	0/3/1	3/7/1	1/9/1
AIF-none	30/31/33	5/5/5	21/21/23	14/15/15	6/5/6	29/31/32	27/28/29	8/8/9	20/21/22	15/15/16
AIF-mild	3/3/1	0/0/0	2/2/0	1/1/1	0/1/0	3/2/1	2/2/1	1/1/0	2/2/1	1/1/0
AIF-moderate	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0
AIF-severe	1/0/0	0/0/0	0/0/0	1/0/0	0/0/0	1/0/0	1/0/0	0/0/0	1/0/0	0/0/0
CIF-none	14/9/16	2/0/2	12/5/9	4/4/9	0/0/0	16/9/18	16/8/12	0/1/6	12/6/10	4/3/8
CIF-mild	11/13/11	2/1/1	3/7/7	10/7/5	0/0/1	13/14/11	8/10/10	5/4/2	2/6/7	11/8/5
CIF-moderate	6/7/7	1/3/2	5/6/7	2/4/2	4/2/5	3/8/4	4/7/8	3/3/1	7/6/6	0/4/3
CIF-severe	3/5/0	0/1/0	3/5/0	0/1/0	2/4/0	1/2/0	2/5/0	1/1/0	2/5/0	1/1/0
SMH-none	0/0/1	0/0/0	0/0/1	0/0/0	0/0/0	0/0/1	0/0/1	0/0/0	0/0/1	0/0/0
SMH-mild	7/16/23	0/4/1	5/13/13	2/7/11	1/4/3	6/16/21	5/15/19	2/5/5	4/11/17	3/9/7
SMH-moderate	14/12/8	0/0/4	7/6/8	7/6/4	2/2/3	12/10/9	11/10/9	3/2/3	12/10/4	2/2/8
SMH-severe	13/6/2	5/1/0	11/4/1	7/3/1	3/0/0	15/7/2	14/5/1	4/2/1	7/2/1	11/5/1
Edema-present	18/18/25	2/3/3	9/15/19	11/6/9	3/5/4	17/16/24	11/16/21	9/5/7	13/13/17	7/8/11

HP: Histopathological, UPJ: Ureteropelvic junction, AIF: Acute Inflammation, CIF: Chronic inflammation, SMH: Smooth muscle hypertrophy, ER: Extrarenal, IR: Intrarenal, CV: Crossing vessel, NIU: Normal insertion of ureter, HIU: High insertion of ureter, LIN: Length on internal narrowing at UPJ

in the result. First, many studies were retrospective and have their weakness related to the data collection. Second, the site of the histology had not been mentioned clearly in the studies and that could change the final assessment. Finally, intraoperative findings, i.e., anatomical variation was not considered or correlated in any of the previous studies except the presence of CV.

Richstone *et al*. defined histologic categories for 95 patients with UPJO including normal or CIF, SMH or atrophy, and fibrosis. Overall, they found that 43% of specimens with a CV had normal histology compared to 10% of specimens with intrinsic aetiology, concluding that patients with a CV were less likely to exhibit 'intrinsic pathologic features'.[7] These findings were very similar to our study results. Similarly, Yiee *et al*. determined that pathologists correctly identified the aetiology of UPJO with CV in 71% of patients and intrinsic in 78% of patients. They found that CV was associated with denser muscle fibres with no change in fibrosis.[8] In contrast, Ellerkamp *et al*. were unable to identify an association between muscle hypertrophy or fibrosis and the existence of lower-pole CV in UPJO.[9] While in our study we found less fibrosis and more CIF in the presence of CV.

The clinical implication of histopathology of CV can be understood by different surgical intervention that has been offered in presence of CV and their different success rates. Gundeti *et al*. found 95% success rate in 20 paediatric patients for vascular hitch procedure for CV.[10] Al-Emadi *et al*. did laparoscopic vascular hitch procedure for polar vessels and found mixed results with 68% success rate.[11] If we consider above mentioned anatomical variations then it could explain partially the low success rate for vascular hitch procedures. Menon *et al*. reported in their study that 24% of CV were associated with intrinsic obstruction and so vascular hitch procedure is not the ideal procedure for all CV.[12]

There is no reported literature that correlates the other intraoperative anatomical variation with the HP findings. The intrarenal pelvis could make the surgical procedure challenging and the extrarenal pelvis could take the brunt of the kidney to prevent or slow the renal damage. But there was no HP parameter that showed any association with the type of renal pelvis.

Another anatomical variation is the high insertion of the ureter (HIU) and it can produce resistance to urinary flow, may undergo external compression and ureteral kinking from an expanding renal pelvis. This aberrant position may also interfere with the peristaltic coordination between the pelvis and ureter, and hinder proper drainage. If HIU was associated with patency of UPJ segment then histopathology was much similar to CV i. e. less fibrosis and more CIF while in cases of HIU with non-patent UPJO there was more fibrosis and more CIF.

The clinical implication of these findings can guide us to understand success rate of different surgical technique described for HIU. Palmer *et al*. did renal pelvis cuff pyeloplasty (the cuff of pelvis with the attached ureter was sutured to the dependent portion of the pelvis) for UPJO caused by HIU and found 100% success rate with proper selection (HIU with patent UPJ) of patients.[13]

There are numerous HP parameters in the literature that have been evaluated in cases of UPJO. These parameters include collagen content of the renal pelvis, arrangement of muscle fibres and nerve fibres, collagen-to-smooth muscle ratio, mean renal pelvis smooth muscle thickness, elastin content, S-100, neuron-specific enolase, and interstitial cells of Cajal.[1-3,5] In our study, we assessed basic HPE parameters because, in the literature, there is no consensus even on a single finding. Future studies can be planned with the above-mentioned parameters for the IOAF association.

The obstructive pathology (intrinsic or extrinsic) at the UPJ triggers some common cascades including the increase in the intrapelvic pressure and inflammatory reaction around the UPJ. The nature of pathology (intrinsic or extrinsic) along with the duration of symptoms lead to final changes over the UPJ region. The contraction of the pelvis against the resistance leads to hypertrophy of smooth muscle cells across all types of UPJO. It was more when there was more LIN and explain that a long segment of resistance leads to more SMH.

According to our study, external pathology like CV, HIU with negotiable UPJ triggers more inflammation and has less fibrosis. While in intrinsic pathology, pre-existing fibrosis is there and it has less potential to trigger the inflammation. Similarly, when the LIN was more, it was associated with more fibrosis and the segment has less potential to generate a strong inflammatory response.

In our study, we mitigated all the confounding factors which were present in previous studies as this was a prospective study with pre-set criteria for the inclusion and exclusion along with marking oriented specimens to a pathologist who was blind for the intraoperative findings. The limitations of our study were the limited number of patients and assessment of basic HP parameters.

Conclusion

All UPJO cases have some common HP changes. The varied intraoperative findings with diverse combinations change the HPE findings in each case suggestive of the distinctive nature of the pathology. Although some particular anatomical intraoperative findings, i.e., presence of CV, negotiable UPJ, HIU and LIN showed association with specific HPE parameters.

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Conflicts of interest

There are no conflicts of interest.

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