Original Article

Role of Interstitial Cells of Cajal in Congenital Ureteropelvic Junction Obstruction

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Abstract

Background: Although congenital ureteropelvic junction (UPJ) obstruction is the most common cause of neonatal hydronephrosis, aetiopathogenesis is still inconclusive. Recently, the paucity of interstitial cells of Cajal (ICC) at the narrow adynamic part of UPJ has been implicated as a causative factor. **Materials and Methods:** This prospective study was conducted between October 2019 and March 2022 to find out the density of ICC by the immunohistochemical method using CD117 (c-kit) antibody, in resected segments of UPJ in obstruction patients and in renal tumour patients as control. ICC/high power field (hpf) was also studied from the margins of the resected segment in the obstruction group. The pre-operative and post-operative sonographic and renal scintigraphic features were compared. **Results:** The median age of patients in the study group (n = 25) was 36 months and in the control group was 39 months. The mean ICC/hpf at the stenotic part of UPJ in the study group was 3.56 ± 1.26 and in the control group was 12.56 ± 1.89 (P = 0.0001). ICC density from the proximal and distal margins of the resected segment was 11.12 ± 2.12 and 11.68 ± 1.62, respectively (P < 0.001). The post-operative antero-posterior diameter of the renal pelvis and differential renal function showed significant improvement in comparison to the pre-operative value (P = 0.0045 and 0.0005, respectively). **Conclusions:** The significant decrease in the density of ICC at the stenotic part of UPJ compared to controls suggests a pacemaker role of these cells in ureteral peristalsis and the aetiopathogenesis of UPJ obstruction. Histopathological analysis of ICC should not only be limited to the stenotic part of UPJ but also should focus on the anastomosed ends of the ureter, which reflects post-pyeloplasty outcome.

Keywords: Anderson–Hynes pyeloplasty, c-kit, hydronephrosis, immunohistochemistry

Introduction

Congenital ureteropelvic junction (UPJ) obstruction is the most common cause of hydronephrosis with an incidence of one in 1000–2000 births.[1-4] There occurs failure of peristalsis to propel urine from the renal pelvis through the ureter downwards.[5,6] Although an adynamic hypoplastic segment at UPJ is the predominant pathology, the aetiopathogenesis is still in debate.[1,5]

Interstitial cells of Cajal (ICC) have been implicated as pacemaker cells that generate slow waves causing smooth muscle contraction, and a decrease in the density of ICC is associated with peristaltic dysfunction.[7-9] These cells express tyrosine kinase receptor c-kit (CD117), which allows them to be visualised by immunohistochemistry.[1,5,6]

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Aim

The present study was conducted to estimate the density of ICC at UPJ in histopathological specimens of UPJ obstruction (UPJO) cases and compare with control groups. The analysis of the study will determine the role of ICC in the pathogenesis and post-operative outcome.

Materials and Methods

This prospective case–control study was carried out in the Department of Paediatric Surgery, after the Institutional Ethics Committee approval and as per the Declaration of Helsinki of

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Ethical Principles for Medical Research. This was conducted between October 2019 and March 2022 on patients operated for intrinsic UPJO. Diagnosis of UPJO was made based on clinical evaluation, ultrasonography and renal scintigraphy. Surgical intervention was performed when there were obstructive features on ultrasonography and delayed drainage or decreased function on the renal scan.

Inclusion criteria

(1) Patients below the age of 14 years with informed consent by parents for the study, (2) children with intrinsic UPJO in whom Anderson–Hynes dismembered pyeloplasty was performed and the resected segment was sent for histopathological study.

Exclusion criteria

(1) Patients with extrinsic or secondary causes of UPJO, (2) patients in whom redo-pyeloplasty was done for failed surgery.

Intrinsic UPJO was confirmed during surgery, and Anderson–Hynes pyeloplasty was performed in all cases. The excisional biopsy sample consisted of a narrow UPJ along with a resection margin of 3 mm above and below the UPJ. Histopathological study was conducted from the stenotic part of UPJ (Section B) and also from the upper and lower margins of the excised segment (Sections A and C, respectively). Sections were stained with haematoxylin and eosin (H and E) followed by immunohistochemistry using CD117 (c-kit) antibody. The total number of CD117-positive cells of Cajal in 10 high power field (hpf) was counted, and the average was calculated to determine the number of CD117 (+) cells/hpf in each case. Patients with extrinsic or secondary causes of UPJO and those with redo-pyeloplasty were excluded from this study.

During the same study period, patients who underwent nephrectomy for Wilms' tumour were taken as the control group, and the excised portion of the ureter at UPJ was sent for histopathological examination. They did not reveal any radiographic features suggestive of UPJO. Post-operative evaluation: patients who underwent dismembered pyeloplasty were followed for clinical signs or symptoms. Ultrasonography and renal scintigraphy were performed between 6 months and 1 year after operation. Surgical success was evaluated by sonographic measurement of the antero-posterior (AP) diameter of the renal pelvis and scintigraphy parameters. The pre-operative AP diameter of the renal pelvis and differential renal function were compared with post-operative measurements.

Statistical analysis

Statistical analysis was conducted using MedCalc Software Ltd, 8400 Ostend, Belgium and The Jamovi project (2023). Jamovi (Version 2.3.26) Sydney, Australia. Comparison of the difference between observed means in two independent samples was checked by the Student's *t*-test. The analysis of variance (ANOVA) test with *post-hoc* analysis was used to compare the means of more than two groups to determine if a relationship exists between them. $P < 0.05$ was considered to be statistically significant.

Results

A total number of 24 cases of UPJO were operated during the study period, out of which one patient had bilateral UPJO (25 renal UPJO units). The patients usually presented with palpable abdominal mass (n = 18, 75%), flank pain (n = 12, 50%) and vomiting (n = 6, 25%). On ultrasonography, the mean pre-operative AP diameter of the renal pelvis was 19.9 ± 6.5 mm (range: 12–40 mm). On renal scintigraphy, the mean pre-operative split renal function was 23.8% ± 6.59% (range: 16%–34%). They underwent dismembered pyeloplasty, and the excised portions of UPJO were sent for histopathological study. During the same period, 16 patients underwent nephrectomy for Wilms' tumour, and the excised UPJ was sent for histopathological study. The demographic features are mentioned in Table 1.

An immunohistochemical study was conducted to determine the distribution of c-kit (CD117)-positive ICC at UPJO in the cases and control groups [Figure 1]. Ten consecutive hpfs were evaluated and counted at the inner border of circular muscle oriented parallel to the muscle fibre. Cells of Cajal are located in the circular muscle layer and are fusiform in shape with a thin cytoplasm and a large oval nucleus. The mean number of ICC/hpf detected from the study group (Section B) was 3.56 ± 1.26, and in the control group was 12.56 ± 1.89 [Figure 2]. Hence, the number of ICC/hpf was lower in the UPJO site in comparison to controls, and the difference was found to be statistically significant (95% confidence interval [CI]: −9.9929 to − 8.0071; $P = 0.0001$).

The mean ICC/hpf detected from the upper (Section A) and lower margins (Section C) of the excised segment from the study group was 11.12 ± 2.12 and 11.68 ± 1.62, respectively. One-way ANOVA (Welch's) revealed that there is a significant difference amongst the three sections A, B and C ($P < 0.001$). *Post-hoc* analysis revealed that both these values are higher in comparison to biopsy samples from the UPJ site (Section B), which revealed significant differences in the distribution of ICC/hpf (95% CI = 6.5683–8.5517 and 7.2947–8.9453 respectively, $P < 0.001$) [Table 2].

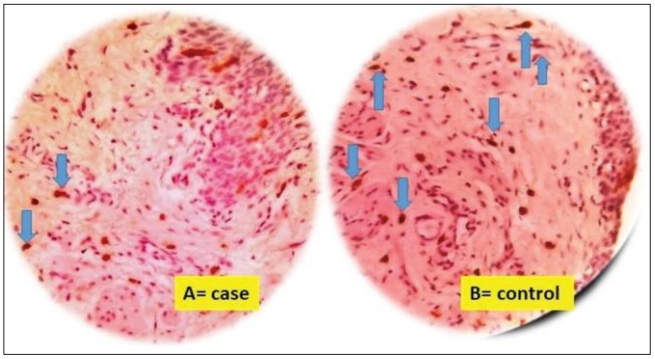


Figure 1: Photomicrographs showing the distribution of c-kit (CD117)-positive interstitial cells of Cajal (ICC) (blue arrows) at ureteropelvic junction obstruction in case (a) and control (b) (IHC, ×200). ICC-positive c-kit cells were fusiform in shape with thin cytoplasm and a large oval nucleus

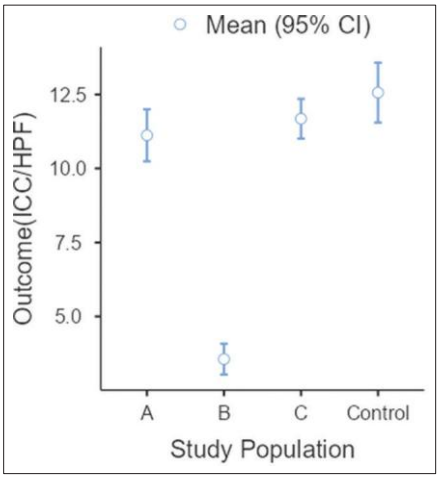


Figure 2: Plot showing the mean (95% confidence interval) distribution of interstitial cells of Cajal/hpf amongst cases and control groups. (A) Section from the proximal margin of the resected segment of the ureter, (B) Stenotic site of the ureter, (C) Distal margin of the resected segment

Table 1: Comparison of demographic features in ureteropelvic junction obstruction cases and controls

Parameters	Study group (*n*=25)	Control group (*n*=16)
Age (months)*	36 (4–132)	39 (4–96)
Sex (male:female)	3:1	1:1
Side of involvement (left:right)	1.8:1	1.3:1

*Median (range)

Table 2: Comparison of means across Section A, Section B, Section C and controls using the one-way ANOVA and Tukey *post-hoc* test

One-way ANOVA (Welch's)				
	F	df1	df2	*P*
Outcome (ICC/HPF)	189	3	43.3	<0.001
Tukey *post-hoc* test - outcome (ICC/HPF)				
	Section A	Section B	Section C	Control
Section A				
Mean difference	-	7.56***	−0.56	−1.443
P	-	<0.001	0.668	0.054
Section B				
Mean difference		-	−8.12***	−9.002***
P		-	<0.001	<0.001
Section C				
Mean difference			-	−0.883
P			-	0.394
Control				
Mean difference				-
P				-

***P<0.001. ICC: Interstitial cells of Cajal, HPF: High power field

During follow-up, all the children in the study group were found to be asymptomatic. Ultrasonography performed between 6 months and 1 year after surgery revealed a mean AP diameter of 14 ± 4.4 mm (range: 9–25 mm). When compared with the pre-operative value, there was a statistically significant decrease in mean AP diameter (95% CI = 1.9713–9.9487, P = 0.0045). Post-operative scintigraphy performed during the same follow-up period detected an increase in mean differential renal function to 31.8 ± 5.7% (range: 26%–41%). The relative improvement of post-operative differential renal function in comparison to pre-operative value was also found to be statistically significant (95% CI = 3.7946–12.3054, P = 0.0005).

Discussion

Although an adynamic hypoplastic segment at UPJ is the predominant pathology seen in intrinsic UPJO, extrinsic compression can be caused by the crossing of vessels and high insertion of the ureter.[1,5,10] Obstruction can also occur secondary to intraluminal foreign bodies, calculus, ureteral valves and polyps.[10] Despite decades of research, the pathogenesis regarding the narrow adynamic segment at UPJ is still controversial.[6,11] The debate revolves around the decreased number of smooth muscle cells, decreased density of ICC, defective innervations, structural disorder of muscle and excessive collagen deposit between muscle fibres.[12-14] The cells of Cajal were first detected in 1893 by Santiago Ramon y Cajal, a Spanish neuroanatomist, and later on, named in his honour.[2,7,15] The pacemaker potential of these cells was first established in gastrointestinal tract motility disorders such as achalasia, congenital hypertrophic pyloric stenosis, Hirschsprung's disease and intestinal pseudo-obstruction.[5-7,16] From the evidence that there occurs a reduction of ICC density in these disorders, investigators searched for their role in the urinary system.[1,6,16] However, in comparison to the association of ICC in gastrointestinal disorders, studies regarding its role on urinary tract disorders are limited.[1,7]

The median age of UPJO cases in our study was 36 months (range: 4–132 months), which is comparable with Nandan *et al*.[11] (median age-36 months, range: 2–140 months) and Eken *et al*.[12] (median age-36 months, range: 3–216 months). However, Pande *et al*.[5] reported an earlier median age of 8.5 months (range: 2–96 months). The male sex predilection (3:1) in our study was also observed by Senol *et al*.[1] (2.8:1), Pande *et al*.[5] (6.5:1), Inugala *et al*.[13] (3.2:1) and Apoznanski *et al*.[17] (1.86:1). Abdominal mass, flank pain and vomiting are common modes of presentation. Infants may be asymptomatic and attending because the diagnosis was made by antenatal ultrasonography.[1,11] This type of presentation was also observed in our study. The predominant involvement of the left ureter (1.7:1) found in this study was also reported in previous studies.[5,10,11]

Our study revealed that the mean number of ICC/hpf is significantly lower in UPJO cases than in the control group. This finding is consistent with previous studies, which made a quantitative comparison of ICC/hpf between UPJO cases and non-UPJO cases [Table 3]. However, the study by Koleda *et al*.[15] provided contradictory results. They found a higher

Table 3: Comparison of studies reporting density of interstitial cells of Cajal amongst cases and controls

Author's place of study	Year (period of study)	Number of cases	Mean ICC/HPF in cases	Number of controls	Mean ICC/HPF in controls	*P*
Senol C *et al*.,[1] Turkey	2015	19	2.3±2.19	12	24.5±9.73	0.0001
Pande *et al*.,[5] India	2020 (June 2016–November 2017)	30	4.86±0.76	7	11.74±0.86	0.04
Eken *et al*.,[12] Turkey	2013	35	5.2±2.1	7	22.7±12.7	0.001
Babu R *et al*.,[18] India	2020 (August 2017–July 2018)	31	5.3±2.3	31	12.4±5.1	0.001
Present study India	2023 (October 2019–March 2022)	25	3.56±1.26	16	12.56±1.89	0.0001

ICC: Interstitial cells of Cajal, HPF: High power field

number of 'fields with many ICC (4-8)' in UPJO specimens than controls. They also found less number of fields with 'few ICC (0-1)' in obstructed specimens than normal UPJ. However, the authors opined that the issue may be due to a compensatory mechanism, as there is obstruction of urine to be propelled. In contrast to our findings, Apoznanski *et al*.[17] reported no significant difference in the distribution of ICC at UPJ between the study group and the control group in UPJO. This may be due to the difference in mean age between the studies and the resultant duration of obstruction. The decrease in ICC density at UPJ in UPJO patients in our study indicates their role in the pathogenesis of the disease. In addition to controls from ureters of Wilms' tumour, we have also evaluated the number of ICC density in normal-looking resected margins of excised ureteric segment in UPJO cases. We found more number of ICC/hpf at both the proximal and distal margins, which is statistically significant ($P < 0.001$) and reflects the quantitative value at the anastomosis site. Recent studies postulated that a decreased number of these pacemaker cells leads to failure of regular and co-ordinated slow waves followed by loss of peristaltic activity.[5,6,11]

During follow-up, there was a significant reduction of the mean AP diameter of the renal pelvis on ultrasonography performed between 6 months and 1 year ($P = 0.0168$). Tokat *et al*.[16] have also detected similar findings in their study. There was a significant improvement in differential renal function postoperatively in our study ($P = 0.0018$), which is similar to previous studies.[16] The higher number of ICC/hpf at anastomosed ends of the ureter (Sections A and C) correlates with post-operative improved outcome in our cases. In our opinion, the unaffected UPJ in the nephroureterectomy specimen of Wilms' tumour is an ideal tissue as the control group. We have taken a reasonable number of controls for comparison, as Wilms' tumours are operated on early in our hospital. This is in comparison to previous studies, where there is a wide gap between the number of cases and controls.[5,11,12,15] The density and distribution of ICC could vary according to age, as reported in some studies and one meta-analysis.[6,12,15] The gross age difference between case and control groups noted in different studies might provide potentially biased result.[5,12,15] However, in the present study, the median age between the patient group and control group is similar, and there is no significant difference.

The ICC density at the anastomotic site is a crucial factor for post-operative outcome. Hence, unlike most of the studies which focused only on the stenotic part of the ureter, we have studied ICC at the proximal and distal resected ends of the ureter and found a significant difference in density from the stenotic site. After pyeloplasty, there was a significant decrease in the mean AP diameter of the renal pelvis on ultrasonography. There was also significant improvement in differential renal function on post-operative scintigraphy. Although some authors opine that the post-operative outcomes are not related to ICC density, they have not analysed quantitative ICC density at resected ends of the ureter.[5,16] However, Inugala *et al*.[13,18] and Babu *et al*.[18] found a correlation between ICC density and clinical outcome, similar to our findings. Inugala *et al*.[13] graded patients with no improvement of drainage and renal function after pyeloplasty as poor outcome. However, all patients in our study group showed significant improvement of radiological and scintigraphic features, which is a reflection of ICC density at an anastomotic site. However, the post-pyeloplasty outcome depends on several factors such as surgical accuracy and the technique of ureteral anastomosis. Pyeloplasty is the standard treatment at present for UPJO. The amount of surgical excision is decided by the visual impression of the stenotic portion at UPJ.[10,13,14] In the future, the extent of distal ureteric resection may be decided by detecting the adequate number of ICC.

The limitations of our study are the limited number of patients and it is a single-centre study. Further multicentre studies with a larger number of subjects will provide more accurate information on these congenital disorders. The strength of the present study is that it has analysed the ICC density at the stenotic site of UPJ in the study group and compared with controls from unaffected UPJ of Wilms' tumour along with both the proximal and distal margins of the resected segment. The present study is the first of this kind where a comparison was made between one study group and three control groups. There was a comparable sample size with no significant age difference between case and control groups. The index study also detected a significant improvement in radiological and scintigraphic outcomes after pyeloplasty. This study will add to the current knowledge regarding the pathogenesis of UPJO and management outcome.

Conclusions

Congenital UPJO is commonly present before 1 year of age with a male predominance and frequent involvement

of the left side ureter. A significant decrease in the density of ICC is marked at the stenotic part of UPJ compared to controls, suggesting a pacemaker role of these cells in ureteral peristalsis and the pathogenesis of UPJO. Normality of ICC at the anastomotic site after resection of the narrow segment in UPJO is associated with post-operative improvement of hydronephrosis and split renal function. Histopathological analysis of ICC should not only be limited to the stenotic part of UPJ but also should focus on the anastomosed ends of the ureter, which will reflect the clinical outcome.

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Conflicts of interest

There are no conflicts of interest.

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