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ORIGINAL PAPER

COLLAGEN DEPOSITION IN SMOOTH MUSCLES OF URETEROPELVIC JUNCTION OBSTRUCTION IN CHILDREN

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Summary

Background. Ureteropelvic junction obstruction (UPJO) is the most common pathological cause of antenatal and neonatal hydronephrosis. In this study we evaluated the proportion of collagen deposition to smooth muscles of obstructed ureteropelvic junction and its relation to the age at the time of diagnosis and to the postoperative complications.

Material and methods. Fifty-five patients diagnosed antenatally or postnatally with idiopathic UPJO were recruited for the study. The age ranged from 1 month to 12 years. All the patients underwent the Anderson and Hynes pyeloplasty and biopsy samples were sent for histopathological examination and collagen assessment.

Results. The median age of enrolled patients was 38.9 (1-144) months. Male to female ratio was 2.1:1. 65.5% patients had UPJO on the left side while 23.6% patients was right-sided and remaining 10.9% cases were bilateral. A significant association was found between collagen

deposition and age at diagnosis. No significant relation was demonstrated between collagen deposition and postoperative complications.

Conclusions. Based on the finding, it could be recommended that management for UPJO should be concentrated at an early age without any delay taking into account the clinical perspectives of various management techniques for the pediatric populations to avoid further complications.

Keywords: Anderson and Hynes pyeloplasty, ureteropelvic junction obstruction, collagen-muscle ratio, postoperative complications, hydronephrosis

Introduction

Ureteropelvic junction obstruction (UPJO) or congenital hydronephrosis is defined as a partial or complete obstruction of urine flow from the renal pelvis to the proximal ureter [1,2] with the incidence rate of 1 in 1000-2000 live births. The UPJO has been considered as the most common obstruction in the upper urinary tract among children. Till date, the pathophysiology of UPJO formation is unknown. It could be due to intrinsic factors such as congenital abnormalities or extrinsic ones following surgery or other conditions such as upper urinary tract inflammation [3].

Various investigations have implicated that anomalies of the structure and ultrastructure of UPJ occur in the condition. Various etiologies have been proposed for UPJO which include the presence of muscle hypertrophy around the distal ureter, changes in the muscular component, deposition of collagen, paucity of smooth muscles along with increased connective tissue [4-6]. Moreover, studies have also shown increased acetylcholine esterase activity and increased noradrenalin response in the condition. Various studies have shown the role of C-kit positive interstitial cells of Cajal (ICCs) as the pacemakers which facilitate the active

propagation of electric events and mediate neurotransmission. Their expression sites in the muscles layer of normal and obstructed UPJO specimens have shown their decreased density in the UPJO, as compared to the normal control group, which could be one of the factors for etiology of UPJO [7,8].

Previous investigations have reported that UPJO is a result of disorientation or absence of smooth muscle fibers (SMF) at the region of ureteropelvic junction with reduction in the nerve terminals and nerves in the region of stenosis, which can result in collagen deposition forming stenotic fibrosis in cases of muscle fibers absence [9].

Collagen deposition and its role in UPJO have been shown by various study groups. It was observed in urine proteome analysis of UPJO patients that there was increased secretion of collagen Vα and IXα3 fragments [10]. Collagen accumulation was also described in experimental unilateral ureteral obstruction rodent model [11]. Kim et al. [12] assessed the role of collagen in UPJO by quantitatively evaluating the ratio of collagen to smooth muscle tissue matrix ratio in UPJO and correlated it with various parameters such as age, and degree of obstruction. It was found that lower tissue matrix ratio showed better functional and morphological improvement of the affected kidney after pyeloplasty. Similar study to determine histopathological changes in the pelviureteric junction in children with obstruction in the pelviureteric junction found that there was no significant change in the wall thickness of pelviureteric junction, mean tunica muscularis in patients with pelviureteric junction obstruction but the collagen thickness values were significantly higher, as compared to the control group supporting the fact that collagen thickness of the ureter is increased in the pelviureteric junctions of children suffering from pelviureteric junction obstruction [13]. Özel et al. [14] in their study comprising 22 children with UPJO found high expression of type 4 collagen suggesting its relation to pathogenesis of UPJO. Abdelnaser et al. [8] in their study evaluated structural changes in muscular, collagenous, and neural components in congenital

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UPJO and found a significant increase in collagen deposition and irregular arrangement of muscle fibers [8]. They also observed disarray of smooth muscle and increased elastin content as the major etiology of UPJO [8]. The studies suggested that collagen-smooth muscle ratio along with the amount of elastin could be a parameter to anticipate recovery length following pyeloplasty. Collagen deposition may be associated with the formation of non-elastic conduit impeding the urine outflow from renal pelvis to proximal ureter and even blocking the downward transmission of urine through the peristalsis of ureter.

Although studies have been conducted to assess the deposition of collagen in UPJO, there are very few detailed studies which assessed whether collagen accumulation is a cause or effect. Keeping this in view, in the study, we tried to figure out the role of collagen accumulation in the UPJO, whether it is a cause or effect. We also examined collagen deposition in smooth muscles of ureteropelvic junction in early and late complication stages among three age groups (less than one year, between 1-4 years and older than 4 years). Further, the total amount of collagen deposited in the smooth muscles was compared at the different sides of obstruction in the ureter.

Aim of the work

The aim of the study is to investigate the role of collagen accumulation in UPJO and determine whether the accumulation is a cause or an effect of the condition. The study seeks to clarify the relationship between collagen deposition and UPJO by examining how collagen levels vary in the smooth muscles of the ureter at different stages of the condition and across different age groups.

Material and methods

The study was conducted at Hevi Tertiary pediatric teaching Hospital in Duhok Governorate in Iraqi Kurdistan which included 55 children suspected to have UPJO from 6th January 2019 to 14th December 2020. Diagnoses were confirmed in all the patients using ultrasound examination (US) and intravenous urography (IVU). Moreover, the voiding cystourethrography (VCUG) was performed to exclude some extrinsic obstructions including vesico-ureteral reflux (VUR) and other lower urinary tract factors responsible for hydronephrosis such as posterior urethral valves. Impacted stones or failed repair of a primary UPJO, VUR, angulations and aberrant vessels, compression by inferior vena cava, pelvic or horseshoe, and duplication anomalies were diagnosed using different clinical and imaging techniques.

All patients underwent loin incision and Anderson and Hynes pyeloplasty. Light microscopy as well as urine culture and sensitivity were performed at the time of skeptical UPJO. Red and/or white blood cells were calculated in the specimens of the complicated cases. The patients with moderate pelvic dilatation (>20mm) and with calyceal dilatation (the anterior-posterior diameter (10-11 mm) of the renal pelvis) were identified as the prognostic limitations.

The surgical techniques were conducted to remove fibrotic and stenotic segments of the obstructions with the formation of a funnel-shaped anastomosis. It was done to fasten the renal pelvis and the ureter as described previously [2]. Resected segments of all the patients were sent for histopathologic examination with additional request to examine collagen content. In all patients, intraoperative J-J stent were placed along with the tube drain in the selected cases. T and J-J stents were removed via cystoscopy two month postoperatively, and patients were followed by monthly ultrasound examination to assess the degree of hydronephrosis and AP

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diameter of the renal pelvis. Monthly general urine examination (GUE) was also done for 6 months and followed by IVU after 6 months of the surgery.

The data of the study was assessed using the Statistical Package for Social Sciences (SPSS) version 23.00. Chi-squared (X^2) and Fisher's Exact Tests were performed in the case of large and small nominal variables in order to evaluate collagen deposition in early and late complication stages among different age groups. The *p*-value equal or less than 0.05 was considered as statistically significant.

Results

Out of the 55 cases of UPJO, 37 (67.3%) were males and 18 (32.7%) females with male-to-female ratio of 2.1:1. Most of the UPJO cases were left-sided viz., 36 patients (65.5%) left-sided, 13 (23.6%) right-sided, and 6 (10.9%) bilateral. The left to right ratio was calculated to be 2.7: 1. At the time of surgery, patients' ages ranged from 1 month to 144 months with a 38.9 months median age (3.24 years old). Twenty (36.4%) patients were below one year of age, 19 (34.5%) were between 1 and 4 years and 16 (29.1%) were older than 4 years.

In 9 (16.4%) patients, there were associated urological anomalies while the remaining 46 (83.6%) cases had no associated anomaly. In majority of the cases, diagnosis was postnatal (43, 78.2%), while in few it was antenatal diagnosis (12, 21.8%). In the early postoperative follow up, 5 patients (9.1%) developed urinary tract infection (UTI), 6 patients (10.9%) developed a leak which resolved spontaneously, and 44 patients (80.0%) did not show any early complications. In the long-term follow-up stage, 3 (5.5%), patients showed stenosis and nephrectomy with the equal percentage and most of them, close to 90% (49, 89.1%), developed no complications.

Moreover, left to right side ratio in male patients were 4.6:1 while in female patients the left to right ratio was 1.14:1. Histopathology of the ureteropelvic junction segments was done for 45 patients, in which 31 patients (68.9%) revealed hypertrophied and decussating muscle fibers, and 14 patients 31.1% revealed collagen deposition beside hypertrophy and decussating muscle fiber (MF) (Table 1).

Table 1. Frequency distribution of UPJO patients' characteristics

Patients' characteristics		Frequency (Percentage)
Patient gender	**Male**	37 (67.3)
	Female	18 (32.7)
Congenital anomaly	**No associated anomaly**	46 (83.6)
	Associated anomaly in the genitourinary system	9 (16.4)
Side of obstruction	**Right**	13 (23.6)
	Left	36 (65.5)
	Bilateral	6 (10.9)
Time of diagnosis	**Antenatal**	12 (21.8)
	Postnatal	43 (78.2)
Early complications	**Infection**	5 (9.1)
	Leak	6 (10.9)
	Normal	44 (80.0)
Late complications	**Stenosis**	3 (5.5)
	Nephrectomy	3 (5.5)
	Normal	49 (89.1)
Histological results	**Muscle hypertrophy and decussating MF**	31 (56.4)
	Collagen fiber replacement	14 (25.5)
	Missed	10 (18.2)
Age group	**Below 1 year**	20 (36.4)
	Between 1-4 years	19 (34.5)
	Older than 4 years	16 (29.1)

Table 2 represents the total collagen content obtained from the histological results and its association with early and late complications, age groups, gender, obstruction side, and diagnosis time. Chi-square tests including chi-square and Fisher's Exact Tests showed that time

of diagnosis of UPJO (antenatal or postnatal) and age groups (below 1 year, between 1-4 years, and older than 4 years) are the only factors that showed a substantial statistical relationship with the positive collagen deposition in smooth muscles, (p=0.02 and p<0.001, respectively). It could be stated that patients older than 4 years or diagnosed postnatally have a greater likelihood of collagen deposition or a more severe health condition compared to those diagnosed earlier and in early age.

No significant association was found between collagen deposition and different early and late complications, patients' gender, side of the obstruction and congenital anomalies, and all complications together as well (p=0.83, p=0.58, p=0.17, p=0.21, and p=0.40, p=0.85 respectively) (Table 2).

Table 2. Total collagen content-related factors in the UPJO

Characteristics		**Histological results**		***p*-value (2-sided)**
		collagen fiber (+)	**collagen fiber (-)**	
Late complications	**Stenosis**	1	1	0.58**
	Nephrectomy	0	3	
	Normal	13	27	
Early complication	**Infection**	1	2	0.83**
	Leak	2	3	
	Normal	11	26	
Patient's gender	**Male**	7	23	0.17*
	Female	7	8	
Side of obstruction	**Right**	2	9	0.21**
	Left	10	21	
	Bilateral	2	1	
Time of diagnosis	**Antenatal**	0	11	0.02*
	Postnatal	14	20	
Age group	**Below 1 year**	0	18	< 0.001*
	Between 1-4 year	4	12	
	Older than 4 year	10	1	
Congenital anomaly	**No associated anomaly**	13	24	0.4*
	Associated anomaly in the urology system	1	7	

Early, late, and no complications	**Early and late complications**	0	2	0.85**
	Early complications	3	4	
	Late complications	1	2	
	No complications (normal)	10	23	

Notes: *Chi-square test and ** Fisher's Exact Test have been performed for statistical significance.

Discussion

It has been well established that UPJO is associated with a significant increase in the intermuscular and intramuscular connective tissue. Studies have also shown increased collagen among the muscle bundles at the obstructed segments. As mentioned above, herein in the present study we aimed at establishing whether the collagen deposition is the cause or effect of UPJO. Moreover, we have attempted to correlate collagen deposition with various parameters including age, gender, and the side of deposition. The study was conducted recruiting 55 patients suspected to have UPJO; they were referred to the Hevi Pediatric Teaching Hospital, the pediatric surgery center in Duhok, Iraq. We found that the rate of UPJO was higher among males than in females (2:1). The finding was in accordance with the previous literature which also showed high male to female ratio [13]. Various other studies, similar to ours showed that UPJO is more commonly seen in boys than in girls [14,15]. We further assessed the side in which UPJO obstruction was present and found that the unilateral left-to-right side ratio was calculated to be 2.7:1. The finding was also in coherence with the previously published data which suggested that majority of the recorded cases of unilateral UPJO were on the left side [15]. In most cases, diagnosis was postnatal whereon only few cases showed antenatal diagnosis in our study cohort. Costigan et al. [16] also showed the similar trend with majority of cases having antenatal diagnosis. However, the pattern was not observed in many studies [15]. Al Aaraj et al. [2] showed that cases which were diagnosed at the prenatal stage were

more numerous, as compared to those at the antenatal stage, but the difference was not significant. We found that nearly 9% of the patients developed UTI as a post-operative complication which has also been reported by previous studies. Roth et al. reported UTI incidence of about five percent in UPJO [17]. According to UPJ muscle layer analysis amongst patients with UPJO, it has been approved that muscle cells are prone to be thinner and fewer in comparison to the healthy subjects. Histopathological study of ureteropelvic junction segments in our study showed that 45 patients were having hypertrophied and decussating muscle fibers in the sections and 14 showed presence of collagen deposition along with hypertrophy and decussating muscle fibers. The collagen content was seen to be deposited in the obstructed part of the ureter in the SMF absence resulting in decrease in the role of ICCs and not allowing the urine to flow from the kidney to the bladder. The finding is in accordance with previously published literature [4,8]. Kim et al. [12] in their study similar to our finding showed that there was a significant difference in the smooth muscle structure component and collagen of the narrowest part of the ureter in the UPJO, as compared to normal conditions [18]. The findings indicate that due to increased collagen, the ureteral distensibility decreases leading to muscle cell damage which further influences contractility.

Conclusions

The confirmation of collagen content deposit in SMFs in the absence or decreases number of ICCs or confers that collagen deposit is considered as a secondary responsible factor to UPJO in ureter. Our study also showed that collagen deposition is not as great in a substantial level in the prenatal and embryotic periods of the age (p=0.020 and p=0.000, respectively). Based on the finding, it could be recommended that management for UPJO should be concentrated at an early age without any delay taking into account the clinical perspectives of

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various management techniques for the pediatric populations to avoid further complications. It is worthwhile to mention that prenatal clinical managements including surgical techniques are not available in Iraq, so it can be focused on early treatment of UPJO directly after birth.

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Ethical approval was obtained from the general directorate of Health of Duhok granted permission for research (14009018-0001on 14 September 2018). Written informed consent was obtained from the parents or guardians of all participants for the use of their medical records, clinical and laboratory data and research publications. Patient confidentiality was maintained by anonymizing all data.

Artificial intelligence (AI) was not used in the creation of the manuscript.

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