

Long-term Outcome of Children with Ureteropelvic Junction Obstruction: Thirty-one years' Experience at a Tertiary Teaching Hospital in South Africa.

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Introduction

Ureteropelvic junction obstruction (UPJO) accounts for up to 62.7% of hydronephrosis, making it the most common pathologic cause of hydronephrosis in childhood (1,2). The incidence of UPJO is estimated at 1 in 1000-2000 live births, with boys more affected in a ratio of up to 4:1 (3,4). The left kidney is more affected (two-thirds of cases), but in 10-46% both kidneys are

involved (5). UPJO occurs mostly sporadically, although autosomal dominant mode of inheritance with variable penetrance has been described (6).

The causes of UPJO are classified into intrinsic and extrinsic (4). Intrinsically, failed recanalization of part of the ureter during embryogenesis causes mechanical obstruction of the affected segment. Smooth muscle

Abstract:

Background and Aim: Being the most common pathologic cause of hydronephrosis in children, we characterized and evaluated the long-term outcome of Ureteropelvic junction obstruction (UPJO) at a tertiary hospital in South Africa

Methods: Children confirmed to have UPJO between 1985 and 2016 were characterized based on demographic and baseline clinical data. Long term outcomes were need for surgical intervention, loss to follow up rates, anthropometric measures, renal outcomes (Glomerular Filtration Rate and Blood pressure).

Results: Of 107 children, 74.8% were male, 47% had hydronephrosis identified antenatally, 47.7% had the left kidney unilaterally affected, 31.8% had an additional urogenital anomaly, 19.6% presented with an abdominal mass, and 37.4% had a urinary tract infection. On enrolment, 54.2% and 30.8% had normal systolic and diastolic BP, 59.8% had normal BMI for age and 72% had normal length/height for age. The median follow-up time was 35(9.0 - 191.0) months, 65% had surgery with a median time to surgery of 2 (0 - 6.8) months. Children lost to follow-up had a higher proportion of extrinsic causes of UPJO (12.0% vs. 0%, $P=0.041$) and other urogenital anomalies (38.7% vs. 15.6%, $P=0.019$). There was no significant effect of time or surgical intervention on mean BMI and height for age, blood pressure percentile and eGFR for age.

Conclusion: In our setting, UPJO has an early presentation, with an early time to surgery. Long-term outcome is favorable, but loss to follow-up presents a significant drawback that needs to be addressed.

Keywords: Ureter; Hypertension; Congenital anomalies of kidney and urinary tract; CAKUT; Urological Diseases; Hydronephrosis.

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hypertrophy and reduced number of nerves and nerve terminals additionally causes functional obstruction (7). Other causes of intrinsic obstruction include polyps, mucosal folds, and persistent foetal convolutions at the upper ureter (8). Extrinsic causes account for 40% of UPJO (4). The most common extrinsic cause is compression of the ureteropelvic junction (UPJ) or upper ureter by a renal vessel that abnormally branches off from the abdominal aorta (9). A highly inserted ureter or abnormally rotated kidney may also cause impaired urine flow resulting in hydronephrosis (10).

UPJO may be associated with abnormalities affecting other parts of genitourinary system: Renal agenesis, multi-cystic dysplastic kidney (MCDK), duplex kidney/collecting system, vesicoureteral reflux (VUR) and posterior urethral valve (PUV) have been reported (11). Occasionally, genetic syndromes increase the risk of UPJO occurring in conjunction with defects involving other systems of the body. Examples in literature include chromosome 17q12 deletion which causes renal cyst and diabetes syndrome (RCAD), chromosome 22q11.2 deletion which causes velo-cardio-facial syndrome, and Chromosome 1q21 deletion which causes abnormalities of the heart and musculoskeletal system(12,13).

Antenatal ultrasound around 18th to 20th week gestational age, while nonspecific in identifying the etiologic cause of hydronephrosis, allows hydronephrosis to be identified while still asymptomatic (14). In the absence of routine antenatal screening, delayed presentation is common (15). Infants typically present with an abdominal mass, but may present with failure to thrive, unexplained fever and recurrent urinary tract infections (4). Flank or abdominal pain caused by distended renal pelvis is the most common presentation in older children (16). The pain is sometimes associated with nausea and vomiting. Hematuria and hypertension are less common presentations (4).

In many instances, confirmation of UPJO as the cause of hydronephrosis is confirmed postnatally with diuretic renal scintigraphy (4). Technetium-99m-mercaptoacetyltriglycine (Tc99mMAG3), 99mTc-diethylenetriamino penta-acetic acid (DTPA), or dimercaptosuccinic acid (DMSA) radionucleotide isotopes may be used. However,

MAG-3 is preferred because of its superior renal secretion properties (17). Other radiographic investigations not commonly used include intravenous pyelography (IVP), computed tomography (CT) scans, and dynamic magnetic resonance urography (4).

The challenge in management of UPJO lies in identifying children at risk of worsening renal function (requiring surgery) from those who will improve or resolve spontaneously (managed conservatively). Published data indicate that even in the absence of surgical intervention, 87% of children with UPJO show improvement in hydronephrosis, grow well and have stable renal function. (18–20). Conversely, deterioration in renal function may necessitate surgical intervention in up to 27% of children (5,21). Understanding the clinical characteristics and the long term outcomes of the whole cohort of children with UPJO regardless of surgical intervention is important in directing management practices. We therefore described the demographic and clinical characteristics, and explored the long-term outcomes of children with UPJO managed at South Africa's Chris Hani Baragwanath Academic Hospital (CHBAH) over the last 31 years.

Methods

Study design

We retrospectively reviewed medical charts of children with a confirmed diagnosis of UPJO in the Department of Pediatrics at CHBAH over the last 31 years, from July 1985 to July 2016.

Setting

CHBAH is one of the tertiary level academic hospitals in South Africa, located in Soweto, Johannesburg. The hospital is a referral center for approximately 3 million people in South Africa, and is one of the teaching hospitals affiliated to the University of Witwatersrand. The Pediatric renal unit receives patients not only from the catchment population, but also from other referring centers in Southern and Central Africa. In the unit, a standardized protocol for management of children with hydronephrosis or suspected UPJO is followed. For antenatal hydronephrosis, a confirmatory postnatal ultrasound is undertaken within 1 month. Suspected UPJO undergoes a screening ultrasound. Grade 3 and 4 hydronephrosis, graded

using Society for Foetal Urology (SFU) grading system(22), is evaluated by diuretic renal scintigraphy. Previously, DTPA/DMSA was used, but currently MAG 3 is preferred. Voiding cystourethrogram is performed for all cases to exclude vesicoureteral reflux. Surgical intervention is indicated for ipsilateral UPJO with differential renal function of less than 40%, bilateral UPJO, recurrent symptoms, and recurrent Urinary Tract Infections (UTI) under antibiotic prophylaxis.

All children with grade 3 or 4 hydronephrosis, bilateral UPJO and those with recurrent UTI are started on antibiotic prophylaxis

Participants

We included all children, aged less than 18 years, with a confirmed diagnosis of UPJO who were managed at CHBAH Pediatric renal unit between July 1985 and July 2016. Records of children presenting with hydronephrosis or features suggestive of UPJO on ultrasound were screened to determine if a confirmatory diagnosis was made. Presence of functionally significant obstruction with differential renal function of less than 40% was considered diagnostic. IVP demonstrating UPJO, CT scan with estimated DRF based on cortical thickness, and MRU demonstrating obstruction were also accepted as confirmatory. Any child without a confirmatory radiologic investigation was excluded.

Variables

Information pertaining to date of birth, date of initial presentation, sex, length/height, weight, serum creatinine level, systolic and diastolic blood pressure (BP) measurements were obtained from the archived medical record for the index and subsequent outpatient visits. We also extracted clinical information on presenting symptoms, surgical procedure done, kidney affected, presence of any other genitourinary anomaly, presence of an extrinsic cause of UPJO, radiologic investigation done, and whether UPJO was part of a known clinical syndrome.

Weight (kg) and length/height (cm) was used to calculate body-mass-index (BMI). BMI and length/height was standardized for age and sex based on the World Health Organization (WHO) and Centre for Disease Control and Prevention (CDC) growth charts (23,24). For children aged less than 5 years, we used the WHO growth charts, while for children older than 5 years we

used the CDC growth charts. Index BMI was stratified into 3 groups: Wasted (<-2 standard deviation), normal (-2 to 2 standard deviation), and overweight (>2 standard deviation) and index height into stunted (<-2 standard deviation) and normal (>-2 standard deviation).

Serum creatinine (Screat) was measured by the National Health Laboratory Service using the Jaffe reaction on a Hitachi cobus c701/702 analyzer (Roche, Germany). Glomerular Filtration Rate (eGFR) was estimated using the updated Schwartz "bedside" formula [$eGFR=0.41 \times \text{Height (cm)}/S_{cr} \text{ (mg/dl)}$] (25). Systolic and diastolic BP was standardized for height, age, and sex based on National High Blood Pressure Education Program (NHBPEP) normative data (26). Index BP was categorized into normal (<90th percentile), elevated (90th to 94th percentile), and hypertensive (> 95th percentile).

For long term outcomes, BMI, length/height, Screat, and BP were recorded as repeated measurement at three time periods (at enrolment, within 1 year of enrolment, and more than 1 year after enrolment). For patients who underwent surgery, the 2nd and 3rd readings were collected after surgery. The arithmetic mean of recorded readings for the time period was used if more than one reading was available. Urine culture results were reviewed, and any growth of a single organism with more than 10⁴ colonies/ml was considered diagnostic of a urinary tract infection (UTI).

Date of last visit and date of surgery was collected to determine duration of follow up and loss to follow up rate, and time to surgery. Children were considered lost to follow-up (LTFU) if they missed their clinical appointment for more than 12 months after the scheduled appointment date. Transfers to adult renal unit or to external health facilities were excluded from this definition.

We compared the demographic and clinical characteristics of children LTFU with children retained in care, and children who had surgery with those who did not.

Data collection

Demographic data, clinical findings, and radiological and surgical reports of children fitting the inclusion criteria was retrieved from the archived clinical files and recorded in an EXCEL data collection sheet.

Sample size

The number of children with a confirmed diagnosis of UPJO during the 31 years determined the sample size. All identified cases who met the inclusion criteria were included.

Ethical Considerations

Ethical approval for the study was received from the University of Witwatersrand Human Research Ethics Committee prior to undertaking the study (Protocol reference number M170532).

Analysis

Data editing and cleaning was undertaken prior to analysis. We used Shapiro-Wilk test and normality curves to analyze data distribution. For normally distributed continuous variables, we described the data using mean and standard deviation. For continuous variables with a skewed distribution, we used median and inter-quartile range. Categorical variables were described using frequencies and percentages.

Differences between the groups were analyzed as follows: Categorical variables were compared using the chi-squared test or Fisher's Exact test as appropriate. For normally distributed continuous variables, we compared mean difference between groups using the student's *t test* or one-way repeated measure Analysis of Variance (RM-ANOVA) for repeated measurement. For continuous variables with skewed distribution, we compared the median difference between groups using the Mann-Whitney test or Kruskal-Wallis test, or Friedman test for repeated measurements. For repeated measurements that were statistically significant, post hoc analysis with Wilcoxon signed-rank tests was conducted with application of Dunn Bonferroni correction, resulting in a significance level set at $p < 0.017$ (27).

Survival analysis to measure duration of follow-up time and time to surgical intervention was done according to Kaplan Meier method. The log rank test was used to determine whether statistical differences existed between compared groups. To determine whether the baseline characteristics might have influenced outcome measures, we compared the outcome variables after adjusting for baseline factors that were found to be significant during bivariate analysis. Statistical significance was determined at $P < 0.05$. SPSS software (version 23.0; SPSS Inc., Chicago, IL) was used for statistical analyses.

Results

Participants

Of the 130 children identified, 107 were eligible. Reason for exclusion is illustrated in Figure 1.

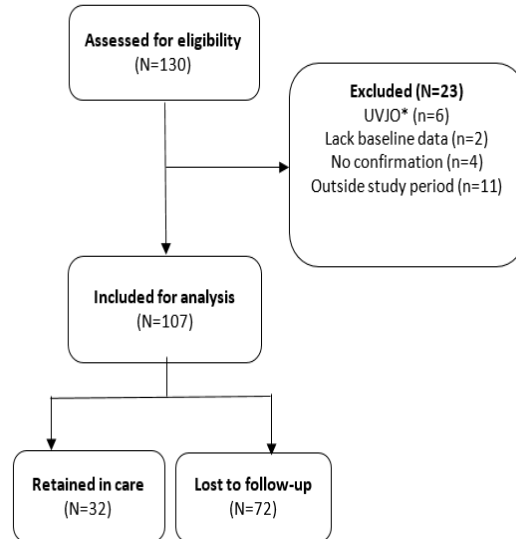


Figure 1. Assessment for eligibility of children with UPJO

Demographic and clinical characteristics at presentation

The characteristics of children with UPJO at presentation is summarized in Table 1. Of the 107 participants included in the analysis, 74.8% (n=80) were male, 59.8% (n=64) had normal BMI for age, and 72.0% (n=77) had normal length/height for age.

Approximately 46% (n=50) of children with UPJO presented with hydronephrosis identified by antenatal ultrasound. The commonest presenting complaints outside the perinatal period were abdominal mass 19.6% (n=21), urinary tract infection 14.0% (n=15), and abdominal pain 11.2% (n=12) (Figure 2). The left kidney was unilaterally involved in 47.7% (n=51) of children while for 16.8 % (n=18) of children both kidneys were affected. In addition to having UPJO, 31.8% (n=34) of the children had a secondary urogenital anomaly, with MCDK being the most commonly associated urogenital anomaly (15.9%, n=17) (Figure 3). For 17.8% (n=19) of the children, UPJO was part of a medical syndrome.

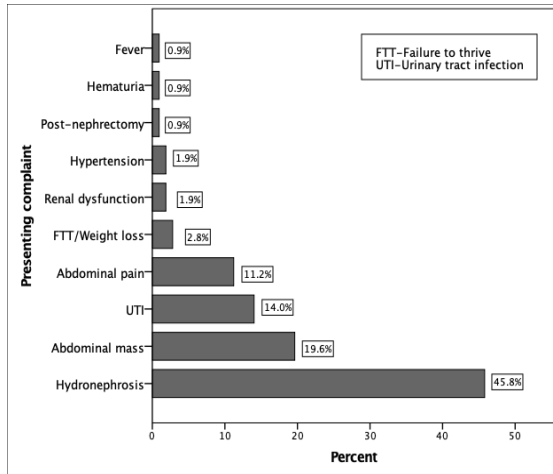


Figure 2. Presenting complaint of children with UPJO

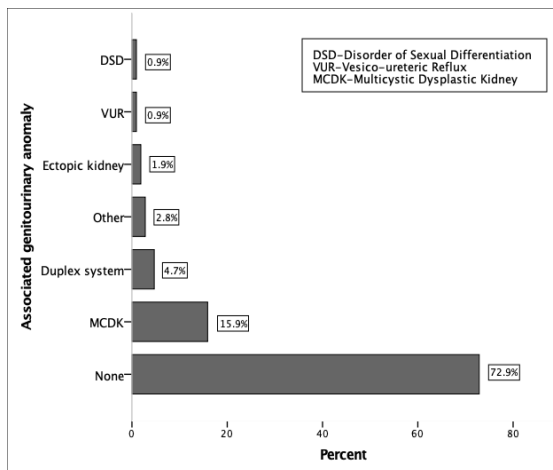


Figure 3. Associated genitourinary anomalies in children with UPJO

MAG3 radionuclide imaging was the most common diagnostic investigation, having been carried out in 60.7% (n=65) of the children (Figure 4). At presentation, 54.2% (n=58) and 30.8% (n=33) of children had normal systolic and diastolic BP, with a mean (SD) eGFR of 64.5 (39.7) mL/min per 1.73 m².

Clinical Outcomes

The median (range) follow-up time was 35 (9-191) months. The cumulative person time in care was 6494 months (541.2 years) resulting in a loss to follow-up incidence rate of 0.010 (0.008-0.013) per person month. Analysis of survival patterns utilizing the Kaplan-Meier method shown in Figure 5 demonstrates that half of the cohort was unaccounted for after about 75

months (6 years) of follow-up. Patients with no surgery had a shorter follow-up duration, with almost 70% of patients being LTFU by 50 months (4 years) (Figure 6).

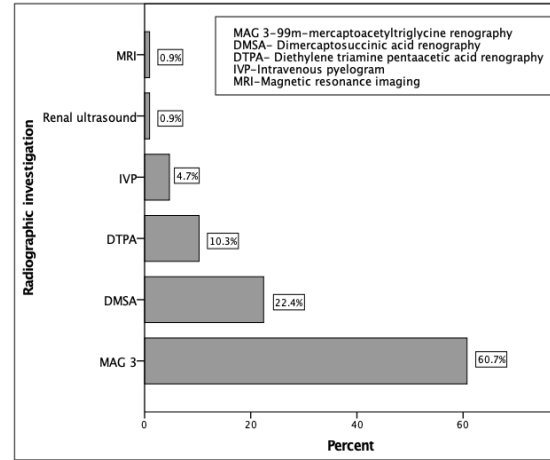


Figure 4. Radiographic investigations for diagnosis of children with UPJO

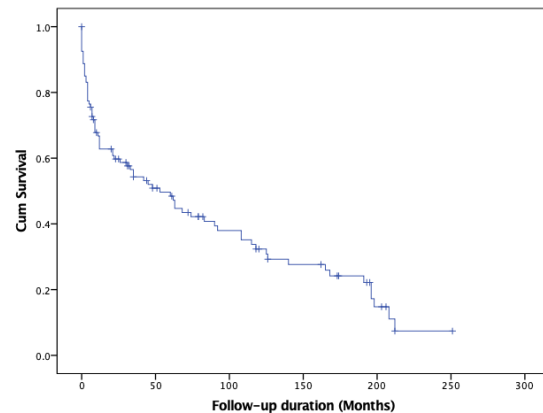


Figure 5. Analysis of duration of time in care for children with UPJO

Sixty-five percent (n=70) of children received surgical intervention with a median time to surgery of 2(0-6.8) months. The commonest surgical procedure was pyeloplasty (n=50, 46.7%), with 13.1% (n=14) of children undergoing nephrectomy.

Urinary tract infection (UTI) was identified in 37.4% (n=40) of children (table 1). More than half (53.8%) were infected multiple times, and *E. coli* was the most common organism cultured in

urine (65.3%) (Figure 7). Only 2.8% of the organisms cultured were resistant organisms. Sixty percent of children (n=65) received anti-bacterial prophylaxis for UTI.

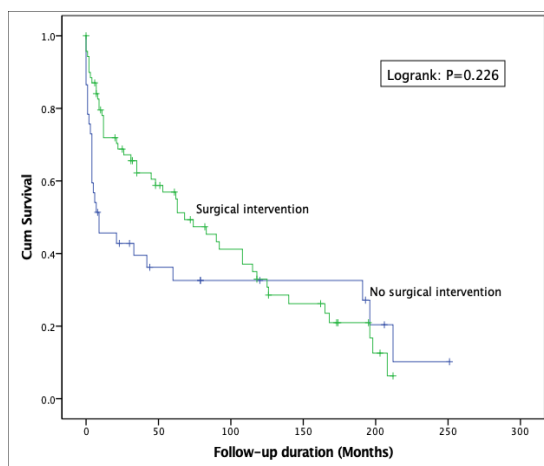


Figure 6. Follow-up duration for surgical and non-surgical groups

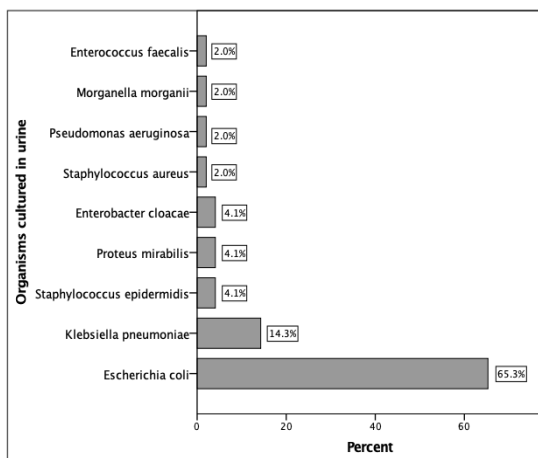


Figure 7. Organisms cultured in children with UPJO who developed urinary tract infection

One way RM ANOVA with Greenhouse Geiser correction determined that there was no statistically significant effect of time on BMI [F (1.6, 86.3)=0.186, P=0.781], length/height [F (1.7,94.2)=3.52, P=0.09], eGFR [F(1.2, 61.0)=0.556, P=0.476], systolic BP [F (1.43, 61.6)=2.850, P=0.810], and diastolic BP [F (1.7, 65)=1.33, P=0.269]. Similarly, there was no significant effect of surgical intervention on any of the variables: BMI [F (1.58, 83.9)=0.465,

P=0.585], length/height [F (2.0, 92.7)=0.29, P=0.710], eGFR [F(1.1, 60.2)=3.155, P=0.780], systolic BP [F (1.4, 14.0)=0.936, P=0.368], and diastolic BP [F (1.7, 63.7)=0.659, P=0.495].

Comparison of children lost to follow-up and those retained in care

Children LTFU had a higher proportion of associated urogenital anomalies (38.7% vs. 15.6%, P=0.019) and extrinsic cause of UPJO (12% vs. 0%, P=0.041). (Table 3)

Comparison between surgically managed and conservatively managed children

The proportion of surgically managed children who had an extrinsic cause was higher than those who were managed conservatively ((12% Vs 0%, P=0.023) (Table 2).

Discussion

The demographic and clinical characteristics of children in our cohort largely mirrors studies reported elsewhere. Our cohort presented earlier but with a high LTFU rate. The time to surgery for those who required it was short, and the long term anthropometric and renal outcomes were favorable regardless of whether surgery was done.

The incidence of UPJO is estimated at 1 per 1000-2000 live births (28). We were unable to determine the incidence of UPJO in our setting due to the retrospective nature of the study. However, we suspect that our study’s sample of 107 children over a span of 31 years is conservative. A substantial number of UPJO might have been missed due to a low number of foetal ultrasounds that were performed. The high LTFU rates also means that some children with hydronephrosis might have been LTFU before confirmation of UPJO.

The epidemiology of UPJO in our cohort mirrors other studies (28). The reason for the male predominance is unknown, and evidence for sex-linked genetic basis is lacking. UPJO is thought to occur sporadically, although autosomal dominant mode of inheritance, localized at 6p human chromosome, has been reported (29,30). The clinical relevance of this localization is still uncertain.

The association of UPJO with other urogenital anomalies may be related to maldevelopment of the genitourinary system during the first trimester. For example, complete obstruction at

Table 1. Demographic and clinical characteristics of children with UPJO retained in care and those lost to follow up

| Characteristic | Overall N=107 n(%) | Retained in care N=32 n(%) | Lost to follow up N=75 n(%) | P value |
|--|--------------------------|-------------------------------------|--------------------------------------|--------------------|
| Sex | | | | |
| Male | 80 (74.8) | 24 (75.0) | 56 (74.7) | 0.971 |
| Female | 27 (25.2) | 8 (25.0) | 19 (25.3) | |
| Weight[†] | | | | |
| Wasted (<-2 z score) | 30 (28.0) | 9 (28.1) | 21 (28.0) | 0.759 |
| Normal (>2 to 2 z score) | 64 (59.8) | 18 (56.3) | 46 (61.3) | |
| Overweight (>2 z score) | 13 (12.1) | 5 (15.6) | 8 (10.7) | |
| Height[†] | | | | |
| Stunted (<-2 z score) | 30 (28.0) | 6 (18.8) | 24 (32.0) | 0.240 |
| Normal (>2 z score) | 77 (72.0) | 26 (81.3) | 52 (68.0) | |
| Symptomatic at presentation | | | | |
| Yes | 58 (54.2) | 13 (40.6) | 45 (60.9) | 0.094 |
| No | 49 (45.8) | 19 (59.4) | 30 (40.0) | |
| Systolic blood pressure[‡] | | | | |
| Normal (<90 th centile) | 58 (54.2) | 15 (46.9) | 43 (57.3) | 0.575 |
| Elevated BP (90 th -94 th centile) | 13 (12.1) | 5 (15.6) | 13 (12.1) | |
| Hypertensive (≥95 th centile) | 36 (33.6) | 12 (37.5) | 36 (33.6) | |
| Diastolic blood pressure[‡] | | | | |
| Normal (<90 th centile) | 33 (30.8) | 9 (28.1) | 24 (32.0) | 0.836 |
| Elevated BP (90 th -94 th centile) | 20 (18.7) | 7 (21.9) | 13 (17.3) | |
| Hypertensive (≥95 th centile) | 54 (50.5) | 16 (50.0) | 38 (50.7) | |
| Type of obstruction | | | | |
| Intrinsic | 98 (91.6) | 32 (100.0) | 66 (88.0) | 0.041 [¥] |
| Extrinsic | 9 (8.4) | 0 (0.0) | 9 (12.0) | |
| Affected kidney | | | | |
| Left | 51 (47.7) | 18 (56.2) | 33 (44.0) | 0.328 |
| Right | 38 (35.5) | 8 (25.0) | 30 (40.0) | |
| Bilateral | 18 (16.8) | 6 (18.8) | 12 (16.0) | |
| Associated urogenital anomaly | | | | |
| Yes | 34 (31.8) | 5 (15.6) | 29 (38.7) | 0.019 [¥] |
| No | 73 (68.2) | 27 (84.4) | 46 (61.3) | |
| Syndromic | | | | |
| Yes | 19 (17.8) | 3 (9.4) | 16 (21.3) | 0.138 |
| No | 88 (82.2) | 29 (90.6) | 59 (78.7) | |
| Surgical intervention | | | | |
| Yes | 70 (65.4) | 22 (68.8) | 48 (64.0) | 0.636 |
| No | 37 (34.6) | 10 (31.2) | 27 (36.0) | |
| Urinary tract infection | | | | |
| Yes | 40 (37.4) | 10 (31.3) | 30 (40.0) | 0.392 |
| No | 67 (62.6) | 22 (68.7) | 45 (60.0) | |
| Age at presentation (months) Median (IQR) | 3 (1-43) | 1 (0-50) | 5 (1-39) | 0.373 |
| eGFR[‡](Mean (SD)) | 64.5 (39.7) | 71.1 (47.9) | 70.0 (36.4) | 0.523 |

[†] Weight and height standardized for sex and age (z scores); [‡]Systolic and diastolic BP standardized for age, sex, and height;

[¥] Statistically significant; [‡] eGFR estimated glomerular filtration rate in ml/min/1.73m²

UPJ prior to 8 weeks of gestation causes dysplasia in the developing kidney which results in MCDK. In a duplex system, UPJO could result from a ureter with a pelvic entry anomaly (31). In our study, 31.8% of UPJO associated with other

renal anomalies is comparable to 27.3% reported in a study by Sharma N et.al. (32). Atiyeh et.al reported a MCDK/UPJO concurrence rate of 12%, which is also comparable to our study (15.9%)(33). The association of UPJO with

Table 2. Comparison of baseline and clinical characteristic of surgery and no surgery group

| Characteristic | Overall N=107 n(%) | Surgery N=70 n(%) | No surgery N=37 n(%) | P value |
|--|--------------------------|-------------------------|----------------------------|--------------------|
| Sex | | | | |
| Male | 80 (74.8) | 51 (72.9) | 29 (78.4) | 0.532 |
| Female | 27 (25.2) | 19 (27.1) | 8 (21.6) | |
| Weight[†] | | | | |
| Wasted (<-2 z score) | 30 (28.0) | 19 (27.1) | 11 (29.7) | 0.931 |
| Normal (>2 to 2 z score) | 64 (59.8) | 42 (60.0) | 22 (59.5) | |
| Overweight (>2 z score) | 13 (12.1) | 9 (12.9) | 4 (10.8) | |
| Height[†] | | | | |
| Stunted (<-2 z score) | 77 (72.0) | 54 (77.1) | 23 (62.2) | 0.080 |
| Normal (>2 z score) | 30 (28.0) | 16 (22.9) | 14 (37.8) | |
| Symptomatic at presentation | | | | |
| Yes | 58 (54.2) | 13 (40.6) | 45 (60.9) | 0.094 |
| No | 49 (45.8) | 19 (59.4) | 30 (40.0) | |
| Systolic blood pressure[±] | | | | |
| Normal (<90 th centile) | 58 (54.2) | 41 (58.6) | 17 (45.9) | 0.411 |
| Prehypertensive (90 th -94 th centile) | 13 (12.1) | 7 (10.0) | 6 (16.2) | |
| Hypertensive (≥95 th centile) | 36 (33.6) | 22 (31.4) | 14 (37.8) | |
| Diastolic blood pressure[±] | | | | |
| Normal (<90 th centile) | 33 (30.8) | 25 (35.7) | 8 (21.6) | 0.071 |
| Prehypertensive (90 th -94 th centile) | 20 (18.7) | 9 (12.9) | 11 (29.7) | |
| Hypertensive (≥95 th centile) | 54 (50.5) | 36 (51.4) | 18 (48.6) | |
| Type of obstruction | | | | |
| Intrinsic | 98 (91.6) | 61 (87.1) | 27 (100.0) | 0.023 [‡] |
| Extrinsic | 9 (8.4) | 9 (12.9) | 0 (0.0) | |
| Affected kidney | | | | |
| Left | 51 (47.7) | 32 (45.7) | 19 (51.4) | 0.656 |
| Right | 38 (35.5) | 27 (38.6) | 11 (29.7) | |
| Bilateral | 18 (16.8) | 11 (15.7) | 7 (18.9) | |
| Associated urogenital anomaly | | | | |
| Yes | 34 (31.8) | 25 (35.7) | 9 (24.3) | 0.229 |
| No | 73 (68.2) | 45 (64.3) | 28 (75.7) | |
| Syndromic | | | | |
| Yes | 19 (17.8) | 13 (18.6) | 6 (16.2) | 0.762 |
| No | 88 (82.2) | 57 (81.4) | 31 (83.8) | |
| Lost to follow-up | | | | |
| Yes | 75 (70.1) | 48 (68.6) | 27 (73.0) | 0.636 |
| No | 32 (29.9) | 22 (31.4) | 10 (27.0) | |
| Urinary tract infection | | | | |
| Yes | 40 (37.4) | 26 (37.1) | 14 (37.8) | 0.944 |
| No | 67 (62.6) | 44 (62.9) | 23 (62.2) | |
| Age at presentation (months) Median (IQR) | | | | |
| | 3 (1-43) | 1 (0-50) | 5 (1-39) | 0.373 |
| eGFR[‡](Mean (SD)) | | | | |
| | 64.5 (39.7) | 71.1 (47.9) | 70.0 (36.4) | 0.523 |

[†] Weight and height standardized for sex and age (z scores); [±]Systolic and diastolic BP standardized for age, sex, and height;

[‡] Statistically significant; [‡] eGFR estimated glomerular filtration rate in ml/min/1.73m²

VUR, on the other hand, is thought to be from disrupted cellular migration and induction events that disrupts proper localization of the future UPJ and VUJ (34). The 0.1% concomitant VUR in our study was significantly lower than the 18% reported by Sharma et.al (34).

Genetic heterogeneity may explain the 17.8% of children with UPJO who had structural anomalies affecting other body systems. Chromosomal microarrays and genetic sequencing has identified more than 40 genomic disorders linked to congenital anomalies of the kidney and urinary

Table 3. Long term outcomes of children with UPJO over three time points

| | Repeated measure estimates | | | P value [†] |
|-------------------------|--------------------------------------|--------------------------------------|--------------------------------------|----------------------|
| | Time 1 [‡] Mean (95% CI) | Time 2 [‡] Mean (95% CI) | Time 3 [‡] Mean (95% CI) | |
| BMI (z score) | 0.15 (-0.49-0.80) | -0.13 (-0.69-0.43) | 0.10 (-0.44-0.65) | 0.781 |
| Height (z score) | 0.23 (-0.43-0.90) | -0.01 (-0.58-0.58) | -0.28 (-0.75-0.19) | 0.089 |
| eGFR[‡] | 60.07 (47.93-72.20) | 64.92 (49.99-79.85) | 70.61 (49.72-91.50) | 0.476 |
| Systolic BP* | 63.76 (54.12-73.39) | 71.34 (63.30-81.35) | 72.83 (64.30-81.35) | 0.810 |
| Diastolic BP* | 82.45 (75.40-89.51) | 78.19 (70.20-86.17) | 73.31 (64.65-81.99) | 0.269 |

[†]Repeated measure ANOVA; [‡]eGFR estimated glomerular filtration rate in ml/min/1.73m²; *BP-Blood pressure in mmHg; CI-Confidence interval; [‡]Time 1 measurement on enrolment; Time 2 measurement within 1 year of enrolment; Time 3 measurement between 1-5 years of enrolment

Table 4. Long term outcomes of children with UPJO over three time points, adjusted for type of obstruction, associated urogenital anomalies

| | Repeated measure estimates | | | P value [†] |
|-------------------------|--------------------------------------|--------------------------------------|--------------------------------------|----------------------|
| | Time 1 [‡] Mean (95% CI) | Time 2 [‡] Mean (95% CI) | Time 3 [‡] Mean (95% CI) | |
| BMI (z score) | -0.09 (-0.65-0.46) | -0.24 (-0.71-0.24) | -0.13 (-0.60-0.34) | 0.585 |
| Height (z score) | 0.36 (-0.20-0.92) | 0.04 (-0.45-0.50) | -0.27 (-0.66-0.13) | 0.714 |
| eGFR[‡] | 60.42 (49.04-71.81) | 63.32 (49.16-77.29) | 66.32 (46.44-86.21) | 0.780 |
| Systolic BP* | 61.52 (52.94-70.11) | 72.23 (65.17-79.28) | 70.93 (63.35-78.52) | 0.368 |
| Diastolic BP* | 80.18 (73.58-86.77) | 76.73 (69.42-84.02) | 73.18 (65.34-81.01) | 0.495 |

[†]Repeated measure ANOVA; [‡]eGFR estimated glomerular filtration rate in ml/min/1.73m²; *BP-Blood pressure in mmHg; CI-Confidence interval; [‡]Time 1 measurement on enrolment; Time 2 measurement within 1 year of enrolment; Time 3 measurement between 1-5 years of enrolment

tract (12). Many of the implicated genes belong to multiple known developmental pathways, and mutations involving any of the genes may affect multiple systems in the body.

The presenting symptom largely depends on the age of the patient. Infants will present with an asymptomatic abdominal mass whereas older children present with mostly pain and urinary tract infection (35). More than half of our cohort (55%) had hydronephrosis detected antenatally. This presentation is in keeping with the younger age of presentation (3 months) and suggests that foetal ultrasound is an effective screening tool for UPJO.

Our findings on renal function is similar to previous studies that show preserved renal function in children with UPJO (5,18–21). Although not statistically significant, there was an upward trend in mean eGFR across the three time periods, with no difference between children who received surgery and those who did not. The observed improvement may be due to spontaneous resolution of hydronephrosis, early surgical intervention, or increased nephron

volume/filtration activity of nephrons in the unaffected kidney (31,36).

Blood pressure (both systolic and diastolic) remained below the 90th centiles across the time periods with no statistically significant change in BP across the three time periods. Unilateral hydronephrosis has been reported to have a low incidence of hypertension due to compensation by the unaffected kidney (36). Surgical correction of UPJO also significantly reduces blood pressure (36). High proportion of unilateral kidney involvement and early surgical intervention could have contributed to normal BP. The high proportion of hypertension in the index BP readings (systolic-33.6% and diastolic-50.5%) was unusual and higher than the general pediatric population in South Africa (24.7%)(37,38). While activation of Renin-Angiotensinogen-Aldosterone and renal sympathetic systems may cause salt-sensitive hypertension in children with UPJO (39), the higher BP in our cohort could be technical. First, diagnosis of hypertension requires BP reading obtained by auscultation. Oscillatory method is widely used in our unit, and

high BP readings are confirmed by auscultation method. There was no record of the method used to obtain BP, and whether all high BP were confirmed. Secondly, white-coat hypertension on anxious children requires ambulatory BP for confirmation which is unavailable in our setting. Thirdly, correct measurement of BP requires a properly-sized cuff, a well calibrated machine, and proper positioning of the child. The retrospective nature of the study precludes us from determining whether the correct procedure was adhered to. Finally, interpretation of BP uses normative data from a different population which is unvalidated in our local setting.

Growth failure in children with chronic kidney diseases is a recognized complication especially in children with hereditary renal disease (40). There was a slight decline in the standardized mean length/height, although this was not statistically significant. Over the evaluated time periods, the standardized mean remained within the normal range. The level of stunting on enrolment is comparable to the national levels of stunting in South Africa (27%) (41). We are however unable to validate that the correct procedure was followed when measuring the length/height, which may be challenging especially in infants. Similarly, the high percentage of wasting on enrolment (28%) is way higher than the national prevalence in South Africa (3%). We are unable to explain this finding and recommend prospective studies which are able to standardize the measurement of weight and length/height. In the long term, however, the mean BMI for age was persistently within the normal Z score, with no statistical difference in BMI for age across the three time periods.

Children with UPJO are susceptible to recurrent UTI, with incidence rates of 15-35% having been reported (42,43). The reported rates are lower than in our study. *Escherichia coli* (*E. coli*) was the most cultured organism. Generally, which was expected since *E.coli* is responsible for up to 80% of UTI in children (42). Antibiotic is usually administered prophylactically to prevent renal scarring. This practice is controversial. Those against the practice propose that the risk of UTI is low regardless of the severity of hydronephrosis(42,44). Our study was limited in examining the temporal relation between

antibiotic use and UTI in children with UPJO as it was retrospective in nature.

Follow-up visits are important in the management of chronic illnesses. Our results demonstrate that even in a predominantly urban population, challenges to follow-up visits exist. Loss to follow-up (LTFU) can compromise a study's validity. In this study, we treated LTFU as a variable to be able to fully describe the cohort of children with UPJO. The high LTFU could be due to a number of reasons. The perceived benign nature of UPJO could explain why caretakers may not see the need for continued follow-up visits. Further, accessibility to our center may present a challenge. Many patients come from far, and the huge financial burden placed by recurrent visits may overwhelm the capacity of care providers. Poor mechanisms to track and follow-up on missed appointments may also contribute to the high loss to follow up. Currently, it is impossible to identify self out-referrals or demised patients. Comparing children LTFU and those retained in care, the two groups were comparable in most aspects, except that extrinsic causes of UPJO and congenital urogenital anomalies were more common in LTFU group. It is possible that the reason for the high LTFU was due to higher mortality rate associated with other congenital anomalies.

Our study had several limitations. Measuring of GFR using either inulin clearance or nuclear medicine-based GFR scans are considered the gold standard. We estimated GFR using the bedside Schwartz method, which while suboptimal, is still acceptable and frequently used in both clinical and research settings. We were however unable to evaluate and demonstrate resolution of hydronephrosis as demonstrated by serial renal ultrasound. We were also unable to evaluate development of albuminuria as an outcome due to insufficient data. The biases inherent in the retrospective design further limited our findings. We couldn't determine cause-effect relationships nor determine the reason for high LTFU rate. Missing data also limited our ability to identify risk factors associated with some of the outcomes seen. Facility-based sampling threatens the external validity of the study since the sample is not representative of the population. The findings contained in this study may not reflect findings of

children with UPJO in other settings. Finally, unlike prospective studies, a retrospective review of records utilizes data collected for clinical purposes. Missing data, and inability to authenticate how the data was collected may be a threat to the internal validity.

Despite these limitations, the study's contribution is appreciable. Our description of this important cohort of children creates a window into understanding children with UPJO in South Africa. With this understanding comes identification of areas that could benefit from improved clinical care as well as areas for further research. An important area of clinical focus includes initiatives to improve patient retention and proper documentation. Enhanced antenatal ultrasound screening may improve identification of children with UPJO, leading to earlier intervention if needed. Follow up research should explore predictors of surgical intervention, predictors of loss to follow up, relationship between prophylactic antibiotic use and development of UTI. Focus on identification of early urinary biomarkers may be of benefit in early diagnosis and management of UPJO.

Conclusion

In our setting, children with UPJO seem to have a favorable clinical outcome. However, the high rate of loss to follow-up makes it difficult to assess mortality rates. High rates of wasting and blood pressure on enrolment needs further evaluation. Randomized control trials and long-term prospective studies are needed to in (validate) high wasting and hypertension rate on enrolment as well as provide high quality evidence to guide management decision.

What is already known on this topic

- Ureteropelvic Junction Obstruction is the most common cause of hydronephrosis in children.
- Antenatal ultrasound is important in identifying perinatal hydronephrosis.
- A large proportion of children with PUJO undergo surgical intervention.

What this study adds

- The epidemiological distribution of Children with UPJO in South Africa.
- Overall, children with UPJO have reserved renal function over time.

- A large proportion of children with PUJO eventually undergoes surgery in our setting.
- Children with UPJO have normal growth (no change in BMI, length/height) over time.
- There is a high rate of follow-up among children with UPJO
- We identified areas that may benefit from prospective studies.

Conflict of Interest

The researchers have no disclosures.

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