



Urinary carbohydrate antigen 19-9/creatinine ratio: A non-invasive marker for follow-up of unilateral ureteropelvic junction obstruction in children

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Summary

Introduction

Ureteropelvic junction obstruction (UPJO) is the most common cause of hydronephrosis in children. One major challenge in the management of UPJO is to select the patients that must be subjected to early obstruction relief. Currently, there is no gold standard for this assessment. Therefore, the aim of the present study was to evaluate the urinary levels of carbohydrate antigen (CA) 19-9 and normalized CA 19-9 (Ca 19-9/Cr ratio) in UPJO patients before and after surgery and compare them with a control group to assess their potential clinical application as an assisting tool in diagnosis of UPJO patients.

Material and methods

From Jan 2013 to Jun 2016, 30 children with history of inguinal hernia, circumcision, hydrocele, and undescended testis as the control group (group 1) and 30 children with unilateral congenital UPJO (group 2) were enrolled in the study. Random CA 19-9 and random creatinine were measured in the voided urine samples of control group and proven

congenital UPJO group preoperatively (group 2A) and at 6 months after dismembered pyeloplasty (group 2B). In addition, the random urinary CA 19-9/CR ratio was evaluated as a marker to normalized urinary CA 19-9.

Discussion

The urinary CA 19-9/Cr ratio was significantly greater in the UPJO group than in the control group. The urinary CA 19-9 also was more in group 2A than in group 1; however, it was not statistically significant. The urinary CA 19-9/Cr ratio and renal pelvis anteroposterior diameter decreased significantly in the group 2B 6 month after complete relief of obstruction in comparison with group 2A preoperatively. Urinary CA 19-9 also decreased in 2B group though it was not significant.

Conclusion

Urinary CA 19-9/Cr ratio is suggested as a non-invasive marker that can assist in diagnosis and long-term follow-up of UPJO patients. This ratio is superior to urinary CA 19-9 as it is more strongly correlated with UPJ obstruction.

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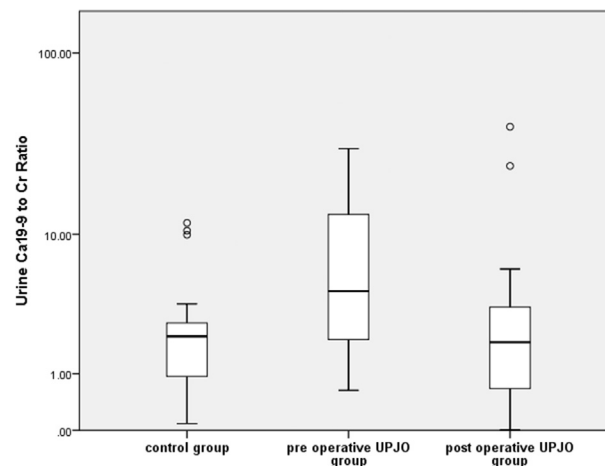


Figure 1 Comparison of urine CA 19-9/Cr in three groups: the pre- and postoperative UPJO groups and the control group.

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Introduction

Ureteropelvic junction obstruction (UPJO), which is functionally defined as a restriction to the urinary outflow, is the most common cause of hydronephrosis in children [1]. From the late 1980s, the management of UPJO has evolved from the surgery of all patients to avoid the potential degradation of renal function into selective operation of them because it has become clear that hydronephrosis does not necessarily mean obstruction [2,3]. This has led to reform of the management of UPJO which currently most clinicians have agreed with close conservative surveillance of newborns with UPJO and referring them for surgical intervention only if renal deterioration is suspected [4] or if there is poor wash out of the radiotracer after furosemide injection, and increasing or grade III and IV hydronephrosis as defined by the Society for Fetal Urology (SFU) [1]. Therefore, one major challenge in the management of UPJO is to select patients who must be subjected to early surgical measures.

Currently, there is no gold standard for the assessment of renal obstruction. The most commonly used tests to assess UPJO are diuretic dynamic renograms using radiopharmaceuticals such as diethylenetriamine pentacetic acid (^{99m}Tc -DTPA) and 3 mercaptyl-acetyl-triglycine (Tc-MAG3) with evaluation of the rate of their pyelo-ureteral washout [5]. Magnetic resonance imaging (MRI) is another modality that could be used for the assessment of renal function and obstruction [6].

CA 19-9 is a tumor-associated carbohydrate antigen discovered by Koprowski et al. [7] using a monoclonal antibody against a human colorectal carcinoma cell line. It is widely used as a tumor marker for pancreatic and gastrointestinal diseases occurring in the gall bladder, pancreas, stomach, colon, bronchial tree, endometrium, salivary glands, and prostate [8–10]. Moreover, expression of CA 19-9 in the normal renal pelvis was reported by Ohshio et al. [11] which was confirmed by case series of hydronephrosis with high serum CA 19-9 levels [12–16]. In recent studies, the urinary CA 19-9 level was also evaluated along with the serum level, which showed relative correlation [17–19]. The non-invasive nature of urinary biomarkers makes them attractive as potential substitutes for invasive methods in the diagnosis and also follow-up of UPJO in the future. Since the urinary concentration of biomarkers can be influenced by urinary dilution, the urinary creatinine (Cr) concentration can be used to normalize their measurement.

The aim of the present study was to evaluate the urinary levels of CA 19-9 and normalized CA 19-9 (Ca 19-9/Cr ratio) in UPJO patients before and after surgery and compare them with a control group to assess their association with renal outflow obstruction and potential clinical application as an assisting tool in diagnosis of UPJO.

Method

From January 2013 to June 2016, 30 children with unilateral congenital UPJO and 30 control children were enrolled in the study. The control children (group 1) were patients with normal abdominal and renal ultrasound who had been referred to hospital for other causes, such as inguinal hernia, circumcision, hydrocele, and undescended testis.

Group 2 consisted of those who were evaluated because of pain, urinary tract infection, or antenatal hydronephrosis. UPJO was suggested by the presence of grade III or IV SFU hydronephrosis on renal ultrasonography. A diuretic renography, using EC (ethylenedicysteine) or DTPA (diethylenetriamine pentacetic acid) scans that showed a $T_{1/2} > 20$ min, a split renal function $< 40\%$, or a decrease $> 10\%$ during follow-up. Vesicoureteral reflux (VUR), as the cause of hydronephrosis, was ruled out by a voiding cystoureterography (VCUG). The exclusion criteria were children older than 15 years old, history of malignant tumors, abnormal liver function, and any benign disease that may have caused elevated serum CA 19-9, such as benign pancreas, lung and liver lesions, diabetes mellitus, chronic renal failure, biliary and inflammatory bowel diseases, and the presence of VUR and bilateral UPJO.

In patients who were toilet trained, voided urine samples were collected by a clean-catch method. In others, an adhesive bag was attached to the perineum after washing and drying the area. Then the caregiver was instructed to check the bag frequently. If the child did not void for 30 min, the bag was replaced with a new one.

Carbohydrate antigen 19-9 was measured using an electrochemiluminescence enzyme immunometric kit (Roche Elecsys Kits) in the voided urine samples preoperatively (group 2A). All patients with proven congenital UPJO underwent dismembered pyeloplasty. Voided urine samples were obtained from these patients at 6 months postoperatively (group 2B). Random urinary creatinine was also measured along with each CA 19-9 measurement. The resolution of obstruction was suggested by a decrease in renal pelvis anteroposterior (AP) diameter on postoperative renal ultrasounds at 1, 3, and 6 months and confirmed by repeating the diuretic renogram at 6 months.

The Ethics Committee approved the protocol, and informed consent was obtained from the parents. Data were expressed as mean \pm SD. Quantitative data were compared between groups by analysis of variance and a paired Student *t* test with $p = 0.05$ as the significance cutoff.

Results

The mean age of patients was 27.43 ± 30.74 months. The comparison of variables in the UPJO group (group 2A) and control group (group 1) is presented in Table 1. Table 2 shows the evaluation of parameters in the UPJO group, pre- and postoperatively (group 2A and 2B). From 30 patients with UPJO who underwent pyeloplasty, 27 were cured of their obstruction and three needed reoperation. In Table 3, the urine CA 19-9, urinary creatinine, and urine CA 19-9/Cr ratio in patients with postoperative non-obstructive and obstructive renal scan are presented. There was a significant difference between the urinary creatinine values in the control and the preoperative UPJO group and it was higher in the control group. Also, the urinary creatinine was significantly higher in postoperative group.

Discussion

Our data showed that CA 19-9 is higher in UPJO group than in the control group, although it was not statistically

Table 1 Urinary CA 19-9 and Cr in UPJO and control groups.

Variable	UPJO group	Control group	<i>p</i>
Urine CA 19-9	116.93 ± 150.87	69.75 ± 75.38	0.13
Urine creatinine	19.03 ± 20.31	34.52 ± 32.11	0.04
Urine CA 19-9/creatinine	8.56 ± 9.08	2.81 ± 2.86	0.004

significant. In addition, this parameter decreased after a successful surgery, as it was shown in other studies that suggested the urine CA 19-9 as a possibly useful marker for post-operative follow up of UPJO patients. In this study normalized urinary CA 19-9, which is the ratio of urinary CA 19-9/urinary creatinine, was evaluated as a marker of urinary obstruction for the first time in the literature. It was higher in UPJO than control group and this parameter was decreased statistically significant in postoperative UPJO patients.

For the first time, some case reports showed that hydronephrosis because of a variety of causes may be associated with high serum CA 19-9 levels [12–16,20]. In these case reports, immunohistochemical testing showed positive carbohydrate antigen 19-9 in the apical surface of cells of the noncancerous renal pelvic epithelium with hydronephrosis [16]. Suzuki et al. [16] have also shown that serum CA 19-9 levels were significantly elevated in patients with benign hydronephrosis. They also showed that the urinary tract infections, proteinuria, increased blood urea nitrogen and urinary tract occlusion were correlated with elevated CA 19-9 [16]. Aybek et al. [17] similarly found that serum and urinary CA 19-9 levels were increased in the hydronephrosis group. They confirmed that there was significant correlation between urinary and serum CA 19-9, but as they acknowledged, the correlation efficient was inadequate to suggest the use of urinary CA 19-9 instead of

serum level. In their study, only symptom duration correlated with elevated urinary or serum CA 19-9 levels, and serum creatinine levels in patients with hydronephrosis and obstruction level or grade of hydronephrosis have not been associated with increased urinary and serum CA 19-9 levels. In the latest studies on this issue, Kajbafzade et al. [18] and Atar et al. [19] published their results, which confirmed the high serum and urinary CA 19-9 levels in UPJO patients compared with the control group and moreover a gradual decrease in both parameters after successful pyeloplasty surgery. They suggested the voided urine CA 19-9 as a non-invasive marker for diagnosis and long-term follow-up of UPJO patients. According to our results, the preoperative urinary CA 19-9 level was higher in UPJO than the control group, but not significantly ($p = 0.13$). However, when this value was normalized for urinary Cr level, the difference became significant ($p = 0.04$). This finding suggests that CA 19-9/Cr ratio may be a better marker for urinary obstruction in our study.

As in other studies, the urinary CA 19-9 in our patients decreased after the relief of obstruction but the difference became significant only when the CA 19-9/Cr ratio was calculated. In addition, we compared these parameters in postoperative non-obstructive and obstructive renal scan groups, which revealed lower urinary CA 19-9 in the former group. The difference, however, was not significant even after normalization of the urinary CA 19-9 level that can be attributed to the low number of recurrent cases (3 patients).

The mechanism of elevated serum carbohydrate antigen 19-9 in cases of hydronephrosis has been explained in previous studies. Immunohistochemical staining in the renal tubulus epithelium, as well as in the urothelium of the renal pelvic were positive for the anti-CA 19-9 antibody [11]. So increased production by the epithelial cells of the renal pelvis and decreased clearance due to urinary tract obstruction may contribute to elevation of serum CA 19-9 level [16]. Shudo et al. [21] also explained that the previous

Table 2 The pre- and postoperative CA 19-9 and Cr in UPJO patients.

Variable	Preoperative UPJO group (N = 30)	Postoperative UPJO group (N = 27)	<i>p</i>
Urine CA 19-9	116.93 ± 150.87	78.80 ± 67.63	0.1
Urine creatinine	19.03 ± 20.31	43.38 ± 25.71	0.0001
Urine CA 19-9/creatinine	8.56 ± 9.08	2.29 ± 2.02	0.0001
AP diameter (mm)	36.32 ± 33.37	14.25 ± 12.56	0.001

Table 3 Comparison of postoperative non-obstructive and obstructive renal scan groups.

Variable	Postoperative non-obstructive (successful) renal scan group (N = 27)	Postoperative obstructive renal scan group (N = 3)	<i>p</i>
Urine CA 19-9	78.80 ± 67.63	109.29 ± 111.88	0.68
Urine creatinine	43.38 ± 25.71	70.70 ± 40.36	0.36
Urine CA 19-9/creatinine	2.29 ± 2.02	1.48 ± 1.03	0.32

hypotheses may be considered the most probable cause of the elevated levels of CA 19-9. A positive correlation was observed between serum CA 19-9 with serum creatinine level [22] and serum BUN [16].

Because the serum CA 19-9 level was supposed to be influenced by renal failure [23], we excluded the patients with renal failure. Our study showed that urinary CA 19-9/Cr ratio may yield a better measure for the presence of obstruction by eliminating the effect of urinary dilution. To our knowledge, this ratio has been evaluated for the first time in our study.

This study has some limitations such as small sample size of groups, lack of serum CA 19-9 measurement in patients and short-term follow-up. These defects request more studies with larger sample size and longer follow up. Moreover, measuring CA 19-9 in patients with non-obstructive hydronephrosis (e.g. in dilating vesicoureteral reflux) is required to prove that the reason for increased level is obstruction and not simply the renal pelvis dilatation.

Conclusion

Our study suggested urinary CA 19-9/Cr ratio as a non-invasive marker for diagnosis and long-term follow-up of UPJO patients that is superior to non-normalized urinary CA 19-9. More studies with larger sample sizes are needed to confirm our findings.

Conflict of interest

None.

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