

Usefulness of basic renal function tests in the management of hydronephrosis

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ABSTRACT

Objective. Nowadays, the algorithms for the study of hydronephrosis in children include voiding cystourethrogram (VCUG) and diuretic renogram (DR) in all patients. Both are invasive, distressing, and associated with radiation risk. However, basic renal function tests (bRFTs) are not included. This study was designed to determine whether bRFTs may help avoid VCUG and/or DR in some children.

Methods. Retrospective review of hydronephrosis (≥ 20 mm renal pelvis) patient records over one year ($n = 38$) (pyeloureteral stenosis (PUS) $n = 12$; high-grade vesicoureteral reflux (VUR) $n = 8$; non-obstructive hydronephrosis (NOH) $n = 18$). Data from the three protocolized bRFTs (maximum urine osmolality after DDAVP (UOsm), albumin/creatinine ratio (Alb/Cr), and NAG/creatinine ratio (NAG/Cr), together with VCUG and DR, were analyzed.

Results. 38 hydronephrosis patients (pyeloureteral stenosis (PUS) $n = 12$; high grade vesicoureteral reflux (VUR) $n = 8$; non-obstructive hydronephrosis (NOH) $n = 18$).

UOsm was decreased in 100% of VUR patients, 75% of PUS patients, and 16.7% of NOH patients. Alb/Cr ratio was increased in 62.5% of VUR patients, 8.3% of PUS patients, and 11.1% of NOH patients. NAG/Cr ratio was increased in 42.8% of VUR patients, 25% of PUS patients, and 6.7% of NOH patients.

UOsm was decreased in most patients who required surgery (100% of VUR patients and 74% of PUS patients), but only in 11.1% of patients who did not (NOH group).

Conclusions. These results suggest that bRFTs may be useful in delaying or avoiding VCUG in some hydronephrosis cases. UOsm is the most sensitive test. No child with (high grade) VUR had a normal UOsm. VCUG could have been avoided in 43% of our patients –with a normal UOsm– without missing any high grade VUR.

KEY WORDS: Hydronephrosis; Renal concentrating capacity; Osmolality; Albuminuria; Vesicoureteral reflux.

UTILIDAD DE LAS PRUEBAS BÁSICAS DE FUNCIÓN RENAL EN EL MANEJO DE LA HIDRONEFROSIS

RESUMEN

Objetivo. Actualmente, los algoritmos para estudiar hidronefrosis en niños, incluyen realizar cistografía miccional (CUMS) y renograma diurético (RD) a todos. Ambos son invasivos, molestos, y con riesgo de radiación. Contrariamente, las pruebas básicas de función renal (PFRb), no están incluidas. Este estudio se realizó para saber si las PFRb, pueden ayudarnos a evitar alguna CUMS y/o RD.

Métodos. Análisis retrospectivo de todas las historias de niños con hidronefrosis (pelvis renal ≥ 20 mm) atendidos durante un año ($n=38$), [estenosis pieloureteral (EPU) $n = 12$; reflujo vesicoureteral (RVU) de alto grado $n = 8$; hidronefrosis no obstructiva (HNO) $n = 18$]. Analizamos las tres PFRb protocolizadas [osmolalidad urinaria máxima tras DDAVP (UOsm), albúmina/creatinina (Alb/Cr) y NAG/creatinina (NAG/Cr)], junto con CUMS y RD.

Resultados. UOsm estaba disminuida en 100% RVU, 75% EPU, 16,7% HNO. Alb/Cr estaba aumentado en 62,5% RVU, 8,3% EPU, 11,1% HNO. NAG/Cr estaba aumentado en 42,8% RVU, 25% EPU, 6,7% HNO. En relación a la necesidad de cirugía, UOsm estaba disminuida en la mayoría de pacientes intervenidos (100% con RVU y 74% con EPU), mientras solo en el 11% de pacientes sin cirugía (HNO).

Conclusión. Estos resultados sugieren que las PFRb pueden ser útiles para retrasar o evitar CUMS en algunos niños con hidronefrosis. La UOsm es la PFRb **más sensible. Ningún niño con RVU (de alto grado) mostró una UOsm normal.** Se podrían haber evitado CUMS en el 43% de nuestros pacientes, con UOsm normal, sin haber perdido ningún diagnóstico de VUR (de alto grado).

PALABRAS CLAVE: Hidronefrosis; Capacidad de concentración renal; osmolalidad; Albuminuria; Reflujo vesicoureteral.

INTRODUCTION

Obstructions and vesicoureteral reflux (VUR) are the most frequent urinary tract malformations associated with hydronephrosis. In these situations, renal function altering mechanisms include hyperpressure in the urinary tract and its association with nephron loss. The latter is caused

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by inadequate *in utero* renal parenchyma morphogenesis, which translates into dysplastic areas of different sizes according to the case. The presence of obstruction brings about a risk of parenchymal atrophy and renal function alteration⁽¹⁾ which, if not properly corrected, will limit the final functional potential of the developing kidney⁽²⁾. A >20mm renal pelvic diameter along with the presence of dilated calyces implies a higher risk of surgery⁽³⁾. There is a third situation with urinary tract dilatation, without obstruction or urine reflux towards the kidney. This is the case of non-obstructive hydronephrosis (NOH), which is known as non-obstructive megaureter when it involves the whole urinary tract.

Current algorithms for the diagnosis of hydronephrosis in children include serial voiding cystourethrogram (VCUG) and diuretic renogram (DR). Both are invasive, distressing, expensive, and associated with radiation risk. However, basic renal function tests (bRFTs) –maximum urine osmolality (UOsm), albumin/creatinine ratio (Alb/Cr), and NAG/creatinine ratio (NAG/Cr), which are cheaper and not distressing, invasive, or associated with radiation risk – are not considered in any protocol published.

Our healthcare facility has been using the three bRFTs, along with imaging tests (VCUG and DR), in the study of hydronephrosis children for years.

This retrospective study was designed to assess the usefulness of bRFTs by comparing data from three groups of children with hydronephrosis caused by three different factors (VUR, PUS, and NOH).

PATIENTS AND METHODS

A retrospective study was carried out by reviewing all histories of children with VUR, PUS, and NOH with a ≥ 20 mm renal pelvic diameter at ultrasound imaging from our hospital's external consultation from January 2016 to January 2017. Inclusion criteria were:

- Availability of, at least, one VCUG and one DR.
- Availability of UOsm and Alb/Cr ratio records – in addition, a NAG/Cr ratio record was available in 30 out of 38 patients.
- Normal creatinine levels for their age. Patients not meeting such criteria were excluded.

A total 38 children (30 males, 8 females) were included (Table 1). Physical exploration was normal in all of them. None of the children had malformation syndromes and they all had an adequate nutritional condition.

In patients having undergone surgery, urine had been collected prior to the procedure.

VUR diagnosis had been achieved using standard VCUG, while PUS had been diagnosed using DR with ^{99m}Tc-MAG3, with pathological response ($T^{1/2}$ over 20 min.). In cases of bilateral VUR, it was included within the highest grade. None of the children had VUR and PUS

Table 1. UOsm, Alb/Cr ratio, and NAG/Cr ratio for the three morphological alterations.

	VUR (n = 8)	PUS (n = 12)	NOH (n = 18)
Age (months)	2 (2.8) (range: 0.13-36)	12 (49) (range: 2.5-126)	14.5 (30.1) (range: 0.13-264)
UOsm (mOsm/kg)	217.7 ± 82.3	633.2 ± 235.0	745.5 ± 154.0
Alb/Cr (µg/µmol)	32.9 (27.5)	2.59 (10.66)	1.9 (2.8)
NAG/Cr (U/g)	30.7 (33.17)	13.5 (11.12)	5.5 (29.93)

UOsm: maximum urine osmolality; Alb/Cr: albumin/creatinine ratio; NAG/Cr: NAG/creatinine ratio; VUR: vesicoureteral reflux; PUS: pyeloureteral stenosis; NOH: non-obstructive hydronephrosis.

concomitantly. All NOH patients had normal VCUG and DR. None of the patients had posterior urethral valves.

Since the objective of this study was to assess the potential usefulness of renal function tests, various clinical aspects such as age at surgery, number of urine infections, or use of antibiotic chemoprophylaxis were not analyzed.

BASIC RENAL FUNCTION TESTS (bRFTs)

In the desmopressin urine concentration test carried out in patients under one year of age, 10 µg of desmopressin were administered intranasally, and the first three urine excretions were collected through urine bags. In patients over one year of age, either 20 µg of desmopressin were administered intranasally, or 0.12 mg (120 µg) of oral lyophilizate (MELT) immediately dissolving in mouth were given. In incontinent children, urine was collected through bags, and in continent children, three urine samples were collected in 90-minute intervals following bladder voiding. The parameter chosen for test result analysis purposes was maximum urine osmolality (UOsm)^(4,5).

Urinary excretion of albumin and N-acetylglucosaminidase (NAG) was calculated using the ratio between the relevant concentrations and creatinine, quantified in a sample from the first urine excretion of the day. The normal values used for the three renal functional parameters studied have been previously published⁽⁶⁾.

LABORATORY TECHNIQUES

Serum creatinine was measured using the creatinase enzymatic method with a Roche/Hitachi Cobas c 701/702 automated analyzer. Urine osmolality was quantified by measuring freezing point depression in an Osmostat Osmome-

Table 2. Qualitative analysis of the three functional parameters studied for the three morphological alterations.

		VUR (n = 8)	PUS (n = 12)	NOH (n = 18)	p
Maximum urine osmolality	Decreased	8	9	3	<0.001
	Normal	0	3	15	
Albumin/creatinine ratio	Increased	5	1	2	0.03
	Normal	3	11	16	
NAG/creatinine ratio	Increased	3	2	1	n.s.
	Normal	4	6	14	

VUR: vesicoureteral reflux; PUS: pyeloureteral stenosis; NOH: non-obstructive hydronephrosis.

ter (Menarini Diagnostics). Albumin was measured using a nephelometric technique (Array). NAG was measured using an enzymatic colorimetric method based on 3-cresolsulfonephthalein-N-acetyl-β-D-glucosaminide hydrolysis (Roche).

STATISTICAL METHOD

The variable with Gaussian distribution (UOsm) was expressed as mean ± standard deviation. Quantitative variables with non-Gaussian distribution were expressed as median and interquartile range. To compare qualitative variable proportions, the Chi-square test with Yates's correction was used. To compare malformations associated with urinary tract hyperpressure and requiring surgery (PUS and VUR) with those not requiring surgery (NOH), sensitivity, specificity, positive predictive value, negative predictive value, and 95% CI odds ratio of the three functional parameters studied were calculated.

<0.05 p values were considered statistically significant. These analyses were carried out using the SPSS (SPSS V 19.0, SPSS Inc., USA) statistical software.

RESULTS

Ultrasound anteroposterior pelvic diameter in VUR children (8M, 0F) was 2.4 (0.88) cm (range: 2-3.2). In six patients, VUR was grade V (three right VUR, one left VUR, two bilateral VUR); in one patient, VUR was grade IV (bilateral); and in one patient, VUR was grade III (right). In this case, as well as in four grade V cases, there was loss of unilateral renal parenchyma (functionally impaired or hypofunctioning kidney). These cases were all treated using ultrasound surgery.

In PUS children (9M, 3F), ultrasound anteroposterior pelvic diameter was 2.45 (1.06) cm (range: 2-3.8). Stenosis was located on the left side in 10 out of 12 cases, on the right side in 1 case, and it was bilateral in 1 case. Children were all treated through open surgery. In NOH patients (13M, 5F), anteroposterior pelvic diameter was 2.35 (0.45) cm (range: 2-5.5). Pelvic dilatation was located on the left

Table 3. Patient distribution in terms of morphological alteration and normality or abnormality of the three functional parameters studied.

	Maximum urine osmolality	Albumin/creatinine ratio	NAG/creatinine ratio
PUS (n = 12)			
n = 3	Decreased	Normal	Normal
n = 4	Decreased	Normal	Not measured
n = 1	Decreased	Normal	Increased
n = 1	Decreased	Increased	Normal
n = 1	Normal	Normal	Increased
n = 2	Normal	Normal	Normal
VUR (n = 8)			
n = 1	Decreased	Normal	Normal
n = 1	Decreased	Normal	Not measured
n = 1	Decreased	Normal	Increased
n = 2	Decreased	Increased	Increased
n = 3	Decreased	Increased	Normal
NOH (n = 18)			
n = 1	Decreased	Normal	Normal
n = 1	Decreased	Normal	Not measured
n = 1	Decreased	Increased	Normal
n = 1	Normal	Normal	Increased
n = 1	Normal	Increased	Normal
n = 2	Normal	Normal	Not measured
n = 11	Normal	Normal	Normal

VUR: vesicoureteral reflux; PUS: pyeloureteral stenosis; NOH: non-obstructive hydronephrosis.

side in 12 out of 18 cases, on the right side in 4 cases, and it was bilateral in 2 cases.

Table 1 features age and results from the three functional tests, distributed according to the three morphological types. In this case, no quantitative statistical study was carried out since ages were different, and normal values for the various parameters studied vary according to age. Therefore, they can only be compared qualitatively.

Tables 2 and 3 feature the qualitative analysis results from the three bRFTs regarding the three morphological

Table 4. Statistical inference and predictive values in two patient groups: patients requiring surgery (VUR + PUS) and patients not requiring surgery (NOH).

	<i>SE</i>	<i>SP</i>	<i>PPV</i>	<i>NPV</i>	<i>Odds ratio</i>
UOsm	85%	83.3%	85%	83.3%	28.33 95% CI: 4.95-162.15 p = 0.0002
Alb/Cr	30%	88.9%	75%	53.3%	3.43 95% CI: 0.59-19.8 n.s.
NAG/Cr	33.3%	93.3%	83.3%	58.3%	7 95% CI: 0.70-69.49 n.s.

UOsm: maximum urine osmolality; Alb/Cr: albumin/creatinine ratio; NAG/Cr: NAG/creatinine ratio; SE: sensitivity; SP: specificity; PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval.

abnormalities. Differences between proportions of the normal and abnormal functional values for each morphological group were statistically significant both in terms of UOsm and Alb/Cr ratio (Table 2).

In the whole sample, UOsm was altered in 20 out of 38 (52.6%) children, while Alb/Cr ratio and NAG/ratio were increased in 8 out of 38 (21.1%) children and in 6/30 (20%) children, respectively.

Regarding alteration, UOsm was decreased in 100% of VUR cases, in 75% of PUS cases, and in 16.7% of NOH cases. Alb/Cr ratio was increased in 62.5% of VUR cases, in 8.3% of PUS cases, and in 11.1% of NOH cases. Finally, NAG/Cr ratio was increased in 42.8% of VUR cases, in 25% of PUS cases, and in 6.7% of NOH cases.

Differences between proportions of normal and abnormal functional values for each morphological group were statistically significant both in terms of UOsm and Alb/Cr ratio.

To calculate diagnostic quality and efficiency of the three functional parameters studied, patients were divided into two morphological subgroups – one for children with potentially surgical malformations (VUR and PUS), and one for patients with no surgical risk (NOH) (Table 4). UOsm's odds ratio was statistically significant.

An inverse correlation was found between UOsm values both in terms of Alb/Cr ratio ($r = -0.67$, $p < 0.001$) and NAG/Cr ratio ($r = -0.59$, $p = 0.001$). In addition, a direct correlation was found between both ratios ($r = 0.71$, $p < 0.001$).

DISCUSSION

VCUG and DR, as well as ultrasound imaging, are included in hydronephrosis study protocols in children⁽⁷⁻¹⁰⁾. However, to our knowledge, there is no protocol

including renal function tests. In our healthcare facility, we have been including both bRFTs and imaging tests for years^(6,11).

This study was designed to verify that severe malformations are typically associated with renal function alterations, to check whether bRFTs can help in the diagnostic process in the absence of severe malformations (NOH), and to assess whether invasive techniques can be delayed and even avoided in some cases.

No functional parameters measuring renal glomerular function such as creatinine or cystatin C were included, since they are highly renal damage specific but little sensitive, and when altered, renal parenchymal damage is already significant⁽¹¹⁾.

It is quite remarkable that all VUR children were male. This has already been described in the literature, which demonstrates that severe VUR grades are more prevalent in male patients, especially when associated with intrauterine renal dysplastic lesions⁽¹²⁻¹⁵⁾.

In our series, VUR patients had the lowest UOsm values, and the highest Alb/Cr ratio and NAG/Cr ratio values (Table 1). However, these differences are not accurate, since those values vary with age, and VUR children were the youngest ones. Therefore, qualitative results are the ones that should be assessed. Statistically significant differences were found between groups, both in terms of frequency of concentrating capacity defect and albumin urinary excretion (Table 2).

VUR is known to be associated with a defect in concentrating capacity directly related to grade and intensity⁽¹⁶⁻¹⁸⁾. In our series, UOsm was decreased in all VUR cases as it is a very sensitive parameter and the cases studied were apparently severe. Concentration capacity defect is related to urinary tract hyperpressure, as it has been experimentally demonstrated⁽¹⁹⁻²¹⁾. UOsm was decreased in 75% of PUS cases, but it barely was in NOH cases (Table 2). Alb/Cr

ratio has also been described to be potentially increased in VUR cases^(22,23). However, such increase is probably more directly related to the loss of existing parenchyma in certain VUR cases (scars and dysplastic lesions) than to urinary tract hyperpressure itself⁽²⁴⁾. Indeed, Alb/Cr ratio was increased in 8.3% of PUS cases only, and in 11.1% of NOH cases. NAG/Cr ratio is a urinary tract hyperpressure marker, although less sensitive than UOsm⁽²⁵⁾, since the excretion of this enzyme is only increased in case of renal proximal tubular cell aggression⁽¹⁸⁾. In our patients, NAG/Cr ratio was increased in 42.8% of VUR cases, in 25% of PUS cases, and in 6.7% of NOH cases (Tables 2 and 3). In conclusion, differences between proportions of normal and abnormal functional values in each morphological group were statistically significant both for UOsm and Alb/Cr ratio.

When dividing patients into those who required surgery (VUR and PUS) and those who did not (NOH), UOsm was the most sensitive parameter in detecting potentially surgical malformations (85%), as well as the highest negative predictive value (83.3%). However, Alb/Cr ratio and NAG/Cr ratio were little sensitive and highly specific (88.9% and 93.3%, respectively), consistent with what has been previously described⁽¹¹⁾. Odds ratio calculation as an estimating factor of probability ratio was statistically significant for UOsm only (Table 4).

The reason why NOH children have certain alterations in bRFTs is unknown, since they technically have a normal parenchyma and no hyperpressure. However, our group has previously noted similar findings in breastfed infants with mild to moderate hydronephrosis⁽⁶⁾. Both patient groups probably have the same abnormalities.

Some of the results previously described are particularly remarkable: 1) UOsm was decreased in all VUR patients (high grade); 2) Most NOH patients had normal values in the three bRFTs (11 out of 15; 73.3%); 3) UOsm was greatly sensitive and had a high negative predictive value; 4) Alb/Cr ratio and NAG/Cr ratio were highly specific. Therefore, in our view, bRFTs and particularly UOsm can be useful in delaying and even avoiding VCUG.

In our series, all VUR children had decreased UOsm. If VCUG had been avoided in all children with normal UOsm (43%), none of the VUR children would have gone undiagnosed. In our series, all VUR cases were high grade cases. If the three bRFTs are normal, and especially UOsm, VCUG can wait. However, this is not valid for DR – if it had been avoided in all children with normal UOsm and even with three normal bRFTs, 2 out of 12 (16.6%) PUS children would have gone undiagnosed, so DR should still be performed even if the results from the three bRFTs are normal.

In our group, none of the children had PUVs. PUV patients tend to have renal damage⁽²⁶⁾, and they always have concentrating capacity defect⁽²⁷⁻²⁹⁾. Therefore, a PUV case would not have gone unnoticed.

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