EVOLUTION OF INDIVIDUAL RENAL FUNCTION IN CHILDREN WITH UNILATERAL COMPLEX RENAL DUPlication

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Objective To assess the evolution of individual renal function during the maturation process in terms of single kidney glomerular filtration rate (SKGFR) and split function in children with unilateral complex renal duplication.

Study design We retrospectively reviewed the records of 44 children with unilateral complex duplex kidney. All affected kidneys had a poor or nonfunctioning dysplastic moiety, 28 in the upper pole and 16 in the lower pole. At least 2 radioisotopic examinations, including a 99mTc-mercaptoacetyltriglycine (99mTc-MAG3) renogram and a plasma clearance of 51Cr-ethylenediaminetetraacetic acid (Cr-51 EDTA), were performed in all children, the first one performed at a median age of 3 months (range 2 to 15 months) and the last one at 24 months (range 12 to 120 months). They allowed a precise estimation of split renal function, overall glomerular filtration rate (GFR), and SKGFR.

Results Mean overall kidney GFR increased significantly between the two measurements from 63 ± 12.7 mL/minute/1.73m² to 95 ± 21 mL/minute/1.73m² (P <.0001). SKGFR of the duplex side similarly increased from 26 ± 7.7 mL/minute/1.73m² to 38 ± 12.6 mL/minute/1.73m² (P <.0001). In terms of split function, the affected kidney had a remarkable stable function between the two measurements, 40% ± 8.6 and 39% ± 8.3 (P = .94), respectively. However, cases with the lowest initial split function (<30%) had the lowest initial SKGFR and the worst further evolution.

Conclusion In children with unilateral complex renal duplication, we found on the affected side a significant increase of SKGFR because of renal maturation, whereas mean split function remained stable during follow-up. (J Pediatr 2005;147:208-12)

Prenatal ultrasonography (US) has resulted in increased detection of duplex systems. We have shown, in a large and unselected population, that dilatations of the fetal urinary tract are associated with complex renal duplication in 4.7% of cases. Actually, with the improving resolution of US equipment, it is possible to differentiate between the two collecting systems, particularly if one is dilated. It is even possible to differentiate between ectopic ureter and ureterocele. This may lead to the discovery of more cases of fetal renal duplications amenable to neonatal management. The present article deals with the estimation of the renal function of this pathological duplex kidney. Split function evaluation is classically obtained from a radionuclide renogram and constitutes a robust and well-standardized measure. However, this only describes the relative function, the behavior of one kidney compared with the contralateral one. Symmetrical increase of renal function related to renal maturation is undetectable using this technique. Similarly, a drop of split function may be a result of either deterioration of unilateral function or contralateral compensation. The combined use of split renal function obtained by means of the renogram and the overall glomerular filtration rate (GFR), obtained by means of the 51Cr-ethylenediaminetetraacetic acid (Cr-51 EDTA) clearance, allows an accurate estimation of the unilateral absolute function in terms of single kidney GFR (SKGFR). In an attempt to clarify the functional behavior of the pathological duplex...

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Cr-51 EDTA 51Cr-ethylenediaminetetraacetic acid
99mTc-DTPA 99mTc-diethylene triamine pentaacetic acid
GFR Glomerular filtration rate
99mTc-MAG3 99mTc-mercaptoacetyltriglycine
SKGFR Single kidney GFR

US Ultrasonography
UTI Urinary tract infection
VCGU Voiding cystourethrography
VUR Vesicoureteral reflux
kidney during the maturation process, we present our experience using this combined approach.

METHODS

Since 1990 we have maintained a registry of antenatally diagnosed urinary tract abnormalities, including renal duplications, in collaboration with colleagues in obstetrics, radiology, and urology. During the last 10 years, 44 consecutive newborns (30 girls) with unilateral severe complex duplex kidney were systematically followed in our department of pediatric uro-nephrology, using the same imaging protocol. Only infants with a poor or nonfunctioning dysplastic moiety were considered for this study.

All babies had serial postnatal US examinations of the urinary tract during follow-up. They also were screened with a voiding cystourethrography (VCUG). Vesicoureteral reflux (VUR) was graded by means of the International Reflux Study Committee classification.5

Radionuclide Studies

All children had at least two radioisotopic examinations during follow-up, the first one performed at a median age of 3 months (range 2 to 15 months) and the last one at a median age of 24 months (range 12 to 120 months). The median interval time between the two studies was 12 months (range 8 to 114 months). Between these two examinations, none of these complex duplex kidneys underwent any surgical procedure, apart from endoscopic incision in cases of ureterocele.

For the renograms, the patient was in supine position and placed above the gamma camera. 99mTc-mercaptoacetyltriglycine (99mTc-MAG3) was administered intravenously at a maximal dose of 100 MBq, scaled on a body surface basis. A 20-minute renogram acquisition was obtained, using 20-second frames. The renal curves were corrected for background using a perirenal area. Split renal function was determined on the basis of the 1- to 2-minute cumulative corrected renal activity, the sum of left and right split function being equal to 100%. The usual range of normality for split function is considered to be between 45% and 55%.7 We considered a 5% change in split function as significant.7 For the evaluation of overall kidney GFR, Cr-51 EDTA was injected, together with 99mTc-MAG3, at a maximal dose of 3.7 MBq adapted to the body surface.8 GFR was determined using a blood sample taken 120 minutes after tracer injection.8 Values, expressed in milliliters per minute, were corrected for body surface. Normal values in function of age have been published previously.9 A 10 mL/minute/1.73 m² change in GFR was considered as significant.9 SKGFR was obtained by combining the split function obtained from the MAG3 renogram and the overall Cr-EDTA clearance, and was expressed in mL/minute/1.73 m². Although the cutoff is probably slightly exaggerated, a similar 10mL/minute/1.73 m² change in SKGFR was considered as significant.

Statistics

Differences between paired samples were determined using Wilcoxon’s signed rank test. A two-sided P value of < .05 was considered statistically significant. The difference between the first and the last measurement was calculated for each duplex kidney. For example, if the kidney uptakes were 48% and 45%, respectively, for first and last measurements, then the difference was noted as 3%. The mean and the standard deviation of these individual differences estimate the systematic bias between the two measurements, whereas the standard deviation of these differences represented the variability between the two successive tests.10

RESULTS

Anomalies Detected

On US scans, all dysplastic moieties showed severe thinning and/or high-grade hydrenephrosis. On 99mTc-MAG3 sequential images, poor or absent uptake in the dysplastic moiety was seen on the early 1- to 2-minute image in 16 lower poles and in 28 upper poles.

Evolution Of Individual Renal Function In Children With Unilateral Complex Renal Duplication

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<th>Table. Functional characteristics of the 44 children presenting unilateral complex duplex kidney during follow-up</th>
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Clinical Evolution and Treatment

**HIGH-GRADE VUR ASSOCIATED WITH NONFUNCTIONING LOWER-POLE SEGMENT.** Sixteen infants (37%) had high-grade (IV-V) reflux into a lower pole on routine neonatal VCUG. These infants were initially managed by medical surveillance and antibiotic prophylaxis. At 2 years of age, reflux ceased spontaneously or decreased in severity in five patients. Three patients underwent lower-pole heminephrectomy for repeated episodes of urosepsis. The other 13 children are still managed non-operatively, and none of them developed symptoms during follow-up.

**URETEROCOELE ASSOCIATED WITH A NONFUNCTIONING UPPER-POLE SEGMENT.** In 16 infants (37%), poor function and
drainage of the upper pole were associated with an ureterocele. Routine VCUG revealed no reflux in 12 patients, isolated low-grade ipsilateral lower-pole reflux in two patients, and contralateral low-grade reflux in two patients. Simple endoscopic incision was performed in all these children. Improvement of upper-pole function did not occur in any patient. In eight patients, iatrogenic reflux developed into the ureterocele and upper-pole segment, in five of them subsequent upper-pole nephrectomy was required for recurrent urinary tract infection (UTI). The remaining 11 children are still managed expectantly. None has required radical surgery or had symptoms of UTI.

NONFUNCTIONING UPPER-POLE SEGMENT RELATED TO URETERAL ECTOPIA OR URETEROHYDRONEPHROSIS. Six children (14%) had an extravesical ectopically inserted upper ureter, and six children (14%) had ureterohydronephrosis. All these children were initially treated conservatively. Upper-pole nephrectomy was required for four children for continuous dribbling incontinence related to an ectopic extravesical ureteric insertion. In the six children with ureterohydronephrosis, four are still managed expectantly and free of medical complications. The two others have required heminephrectomy for recurrent UTI.

Functional Differences Between First and Last Measurements

The 44 duplex kidneys had a remarkable stable mean split function between the two measurements, 40% \( \pm \) 8.6 and 39% \( \pm \) 8.3 \( (P = .94) \), respectively (Table). Taking into account the criteria of normality, 17 of these 44 duplex kidneys (39%) had a normal split function value \( (\geq 45\%) \) on the first measurement.

In Figure 1, a Bland and Altman plot shows the individual differences between first and last split function value in function of the mean split function values on the duplex side. The mean of these differences was equal to \(-0.9\%\), and the standard deviation of these differences, representing the variability of these differences, was 2.3%. For only one duplex kidney was the difference between the two successive measurements \( >5\% \) (a 7% decrease between first and second measurement).

For the whole group of 44 patients, the mean overall GFR increased significantly between first and last measurements from 63 \( \pm \) 12.7 mL/minute/\( 1.73m^2 \) to 95 \( \pm \) 21 mL/minute/\( 1.73m^2 \) \( (P < .001) \). When combining GFR with split function, a similar trend was found in terms of mean SKGFR on the duplex side from 26 \( \pm \) 7.7 mL/minute/\( 1.73m^2 \) to 38 \( \pm \) 12.6 mL/minute/\( 1.73m^2 \) \( (P < .0001) \), the mean value of SKGFR on the diseased side being lower than on the contralateral normal side \( (P < .0001) \).

The individual differences between first and second SKGFR measurement were compared with the corresponding differences between first and second split function values (Figure 2). Among the 44 duplex kidneys, a significant SKGFR increase was observed in 27 (61%) cases. In six cases, this increase was even higher than 20 mL/minute/\( 1.73m^2 \).

When split function on the duplex side was \( <30\% \) (six duplex kidneys), the corresponding SKGFR was systematically low with values between 9 and 20 mL/minute. Moreover, the further evolution of SKGFR was unfavorable: SKGFR did
not improve except in one case with a SKGFR increase from 18 to 28 mL/minute/1.73m² (Figure 3). It is to be mentioned that the size of all these kidneys on US was systematically small and below −2 standard deviation according to chronological age.¹¹

When initial split function was higher than 30% (38 duplex kidneys), the corresponding SKGFR was almost superior to 20 mL/minute/1.73m². In 68% (n = 26) of these duplex kidneys, SKGFR increased significantly, from +10 to +47 mL/minute/1.73m². However, in 32% (n = 12) of these duplex kidneys, SKGFR did not improve (Figure 3). Among this group, three children had already reached adult levels (between 40 and 54 mL/minute/1.73m²) at the first isotopic examination, thus explaining the absence of further significant increase of function.

Finally, the evolution of SKGFR was not related to the specific pathology affecting the diseased moiety.

**DISCUSSION**

The classic radiological work-up of duplex kidneys is based on US and VCUG.¹²,¹³ The aim of US is to assess the urinary tract morphology, whereas the role of VCUG is to demonstrate the presence of VUR and to visualize the bladder and the urethra.

Isotope studies are mandatory to determine renal function that remains in the dilated and dysplastic renal moiety. Most people agree that the surgical approach to complex duplex systems is largely predicted on the function of the affected renal moiety and the presence or absence of function.¹⁴ Confusingly, despite the wide use of radionuclide renogram by the majority of pediatric nephrologists and urologists in the management of these children, little is known about the evolution of the functioning moiety. In our opinion, the present study provides what may be the true account of the natural history of unilateral function in infants with unilateral complex duplex kidney during the maturation process.

Split function calculated on the early images of a ⁹⁹mTc-MAG3 renogram is a robust and well-standardized technique allowing the determination of the relative function with a precision of 5%. In pathological duplex kidneys, it was conceivable that a decrease of split function would have been observed during development, either because of degradation of the function of that kidney or because of an asymmetrical maturation of the function, with or without functional compensation, on the contralateral normal side. To understand the mechanism involved, we evaluated the absolute function of each kidney.

GFR determination based on the injection of a glomerular tracer such as ⁹⁹mTc-DTPA or Cr-51 EDTA, associated with measurement of residual activity in plasma samples has been shown to be accurate, closely correlated with inulin clearance and reproducible.¹⁶ Simplified methods using two or even one blood samples have almost the same accuracy and reproducibility as the evaluation of the entire plasma disappearance curve by means of multiple blood samples.⁸ Simple algorithms are available in both adults and children and are well accepted in international consensus guidelines.¹⁵

The method used in the present work is based on a single blood sample at 120 minutes and allows accurate estimation of overall GFR in children.⁸ As long as no renal insufficiency is present, which was the case in our series of patients. To estimate the absolute function of each kidney, the overall Cr-51 EDTA GFR was combined with the split function determined on the renogram. One could argue about the use of a tubular tracer such as ⁹⁹mTc-MAG3 to estimate split glomerular function. There are indeed some theoretical considerations suggesting that a change in filtration fraction observed in some diseases may result in a split function different for a tubular tracer and for a glomerular tracer. There is however no hard clinical or experimental evidence in the literature showing clearly this discrepancy in subjects without acute obstruction. On the contrary, it has been shown using ⁹⁹mTc-MAG3 as tubular tracer and ⁹⁹mTc-DTPA as glomerular tracer simultaneously, that both split functions are almost identical in a large group of adult patients with various urorheological diseases and a wide range of split function.¹⁷ Thus, unless new data in the future contradict the present option, the combined use of ⁹⁹mTc-MAG3 split function and overall Cr-EDTA clearance is presently, in our opinion, the most accurate and simple way to get the absolute function of each kidney.

After correction for body surface area, we found a significant increase in overall GFR between the two measurements (Table). There is therefore no doubt that significant maturation of the renal function occurred in these children followed conservatively with prophylactic antibiotics, between a median age of 3 and 24 months.

Several authors have shown that a malfunctioning kidney will try to compensate for the loss of renal function by glomerular hyperfiltration of the remaining tissue and/or by mobilizing at least a part of its functional reserve.²⁰,²¹ One can therefore make the hypothesis that during the renal maturation process that normally occurs during the first 15 to 18 months of life, the maturation of the diseased kidney will be less than the normal one. In the present study, we did not intend to evaluate the long-term effects of chronic hyperfiltration on the duplex kidney. The aim of the study was to observe what is happening during the maturation process. Our expectation was to see a progressive unbalancing split renal function as a result of an impaired maturation process on the duplex kidney in relation with the loss of functional parenchyma, together with a possible contralateral compensation. Surprisingly, no significant change of split function was observed during the follow-up, suggesting a symmetrical maturation of the unilateral function (Table).

Furthermore, our results suggest that an initial split function >30% was generally associated with the highest initial SKGFR values and a significant further increase of this. Such a high initial split function was however unable to predict the unfavorable evolution of SKGFR in about one third of the cases.

In contrast, the cases with the greatest initial functional impairment had a poor potential of improvement. Duplex...
kidneys with the lowest initial split function (<30%) had the lowest initial SKGFR and the worst further evolution.

REFERENCES