

Relationship between renal apparent diffusion coefficient values and glomerular filtration rate in infants with congenital hydronephrosis

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Summary

The aim was to investigate the relationship between apparent diffusion coefficient (ADC) values measured by diffusion-weighted magnetic resonance imaging (DW MRI) and the split glomerular filtration rate (GFR) in infants with congenital hydronephrosis. Diffusion-weighted imaging (DWI) ($b = 0$ and 700 seconds/mm^2) was performed with a General Electric Company (GE) Signa 1.5T MR unit in 46 infants suffering single congenital hydronephrosis and in 30 healthy infants as normal control group. The ADCs were calculated with regions of interest (ROIs) positioned in the renal parenchyma. The 46 obstructed kidneys were classified into four groups according to the GFR level: renal dysfunction compensated group, renal dysfunction decompensated group, renal failure group, and uremia group. The renal ADCs in six groups (normal kidneys in control group, contralateral kidneys, and four groups of hydronephrotic kidneys) were compared statistically using analysis of variance (ANOVA), and the correlative relationship between ADCs and GFR was examined by Pearson's correlation test. There were statistically significant differences in renal ADCs among the six groups. The ADCs of hydronephrotic kidneys were lower than that of the normal kidneys. There was a moderate positive correlation between the ADCs of hydronephrotic kidneys and split GFR ($r = 0.744$). This study indicated that the ADCs of congenital hydronephrotic kidneys were lower than that of normal renal parenchyma, and there was a positive correlation between the ADCs and split renal GFR, which demonstrates that the ADCs can reflect the filtration function of hydronephrotic kidneys and may provide some reference to help clinical physician to explore a novel noninvasive approach to evaluate the single renal function.

Keywords: Congenital hydronephrosis, glomerular filtration rate, apparent diffusion coefficient, magnetic resonance imaging, diffusion-weighted imaging

1. Introduction

Obstruction at ureteropelvic junction, often referred to as congenital hydronephrosis is a common disease for infants with 0.13-0.16% incidence (1). It is essential for the clinical physician to understand the morphology and the function of hydronephrotic and contralateral kidneys in order to choose the appropriate clinical therapeutic

protocols. Currently, it is debatable in the determination of the function of hydronephrotic kidneys, and there is still no satisfactory non-invasive diagnostic method to evaluate the damage degree of unilateral involved kidney and to predict the restoration of renal function after operation.

Diffusion-weighted magnetic resonance imaging (DW MRI) is a technique used to measure and image the diffusion of water molecule, can reflect Brownian motion of water molecule in tissue and serve as a functional imaging to represent the functional condition of living tissue *in vivo*, which is a hot research area in recent years. Apparent diffusion coefficient (ADC) is a quantitative index for diffusion-weighted imaging (DWI), can provide the quantification standard for

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disease diagnosis through the different ADC values in diverse pathological changes.

With affluent blood supply and highly water-contained content, kidneys are one of the ideal organs for DWI examination in abdominal viscera (2,3). Considerable attention has been made to investigate the renal DWI across the world (4-6), and some recent studies had demonstrated that the DWI has potential clinical value in evaluating some renal diseases (7-10), such as renal artery stenosis, diffuse renal disease, renal tumor and renal infection (11-15), etc. However, as a novel functional imaging for the investigation of renal function, the DWI is mainly applied in adult patients and the studies focusing on renal diffusion of infants is scarce, and no study at present was found with regard to using renal ADC values to explore the hydronephrotic kidney in single children population. Some research found that the renal ADC values of infants would change considerably when age increases, and there is significant difference of renal ADC values among different age groups (16). As such, the aim of our study is to investigate the relationship between renal ADC values measured by DWI and glomerular filtration function in infants with congenital hydronephrosis, and the clinical application value of using renal ADC values to evaluate the renal function in hydronephrotic kidneys, with the expectation to provide evidence to help physician to find out a novel noninvasive approach of evaluating the split renal function in clinical practice.

2. Materials and Methods

2.1. Research subjects

Patients group: 46 infants suffering single hydronephrosis caused by congenital obstruction at ureteropelvic junction, between October 2008 and October 2009 (12 women and 34 men, age range is between 5 months to 3 years, mean age = 1.9 years), were included in our study, and all patients were diagnosed with ultrasonography, intravenous urography (IVU) and magnetic resonance urography (MRU), 26 of whom were confirmed by operation. Renal dynamic scintigraphy (^{99m}Tc -DTPA, HTA CO. LTD., Guangzhou, Guangdong, China) was used to measure the split renal glomerular filtration rate (GFR) for all patients within one week of MRI examination and the field of view (FOV) included both kidneys. Dynamic collection was performed immediately after "bolus" intravenous injection of ^{99m}Tc -DTPA and the split GFR was calculated separately. The patients were divided into four groups according to degree of renal insufficiency: renal dysfunction compensated group (reduced GFR but is greater than 50 mL/min, serum creatinine and blood urea nitrogen are normal, 9 cases), renal dysfunction decompensated group (25 mL/min \leq GFR < 50 mL/min, 13 cases), renal failure group (10 mL/min \leq GFR

< 25 mL/min, 21 cases), and uremia group (GFR < 10 mL/min, 3 cases). No obviously abnormal features were observed in 46 kidneys in the contralateral side assessed by ultrasound, IVU and MRI.

Control group: 30 normal and healthy infants (8 women and 22 men, age range is between 4 months to 3 years, mean age = 1.7 years) were selected randomly. Inclusion criteria: (i) no clinical history of renal diseases; (ii) no present clinical manifestations of renal diseases; (iii) all the laboratory results related to renal function are normal, which mainly include serological examinations (such as blood urea nitrogen, uric acid, creatinine, potassium, sodium, chloride, etc. that are relevant to the renal function) and routine urine test; (iv) normal report of kidneys by MRI; (v) no medication that may significantly affect renal function has been taken.

This study included six groups (normal kidneys in control group, contralateral kidneys, and four groups of hydronephrotic kidneys), and it was reviewed and approved by the Hospital Ethics Committee, and all the parents of the study subjects have signed informed consent form before the examinations.

2.2. MRI examination method

MRI examination was performed with a 1.5T MR imager (Signa; General Electric Company (GE), USA) with Torso phased-array coil. Before the examination, keep the stomach empty for 6 h and all the subjects were given sedative orally (10% chloral hydrate, Zhujiang Hospital, Guangzhou, Guangdong, China; 0.5 mL/kg.). During the examination, the subjects were dormant lying on the examining table and respiration was monitored by respiratory gating technique. The upper abdominal axial routine scan was performed (T_1 weighted imaging, T_2 weighted imaging, MRU and DWI), and the range included the long diameter of bilateral kidneys. Single shot spin-echo echo-planar imaging (SE-EPI) sequence was applied in DWI examination. Scan parameters: TR 3000ms, TE 6.6-70.5ms, FOV 30 cm \times 30 cm, reconstruction matrix (RES) 128 \times 128, thickness = 4 mm, interval = 1 mm, NEX 8. Three directions of diffusion were measured simultaneously with two b values selected as 0 s/mm² and 700 s/mm². Fat suppression was applied during the scan.

2.3. Images review and post-processing

The original data collected during the scan were transmitted to the post-processing workstation, and the DWI and ADC maps were automatically reconstructed using GE Functool software with ADC values of renal parenchyma being measured at ADC map. Given the low signal to noise ratio in EPI image, it is difficult to clearly differentiate the renal cortex and medulla. In order to reduce measurement errors, in this study,

the ADC values were measured on the whole renal parenchyma. Three planes, including the upper pole of kidneys (4-6 mm from renal upper border), renal hilum and lower renal pole (4-6 mm from renal lower border), were selected in each subject. Two regions of interest (ROIs) of each plane were delineated by two senior radiologists. The average area of the ROIs was about 25 mm², and the mean value was considered the final ADC value. The renal ADCs in six groups (normal kidneys in control group, contralateral kidneys, and four groups of hydronephrotic kidneys) were calculated.

2.4. Statistical analysis

Statistical analysis was performed with the SPSS 16.0. The significant differences of the renal ADCs values in six groups were assessed using completely randomized variance analysis (ANOVA), and the least-significant difference (LSD) method was used to compare the difference of ADC values between each two groups. The relationship between the renal ADC and split GFR was examined by Pearson's correlation coefficient

test. A *p*-value < 0.05 was considered statistically significant.

3. Results

The DWI images of all subjects were in accordance with the diagnosis standards without obvious distortion and artifacts (Figures 1-4).

The mean renal ADCs of six groups (normal renal parenchyma in control group, contralateral kidney group and four hydronephrotic kidney groups) were shown in Table 1. Significant difference was found between different groups (*F* = 148.46, *p* < 0.001). The renal ADCs in renal dysfunction compensated group were lower than that of contralateral kidney group, and the latter is lower than that of normal renal parenchyma in control group.

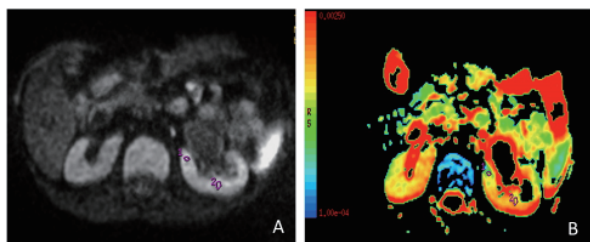


Figure 1. DWI (A) and ADC (B) map of a 36-month-old male infant with left-side congenital hydronephrosis belonging to renal dysfunction compensated group. Two ROIs in the parenchyma on the renal hilum section were delineated by two senior radiologists, and the average area of the ROIs was about 25 mm², and the mean value was considered the final ADC value.

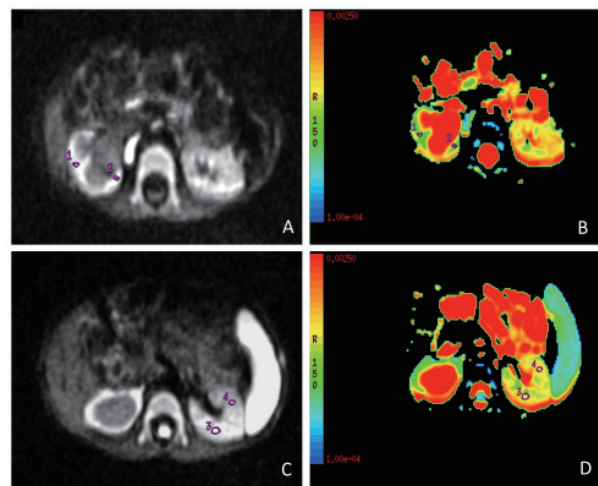


Figure 3. DWI (A, C) and ADC (B, D) map of a 24-month-old female infant with right-side congenital hydronephrosis belonging to renal failure group. The ADC value of the two renals was calculated alone.

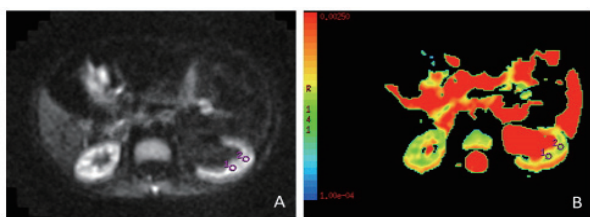


Figure 2. DWI (A) and ADC (B) map of a 36-month-old male infant with left-side congenital hydronephrosis belonging to renal dysfunction decompensated group. ROIs are manually delineated.

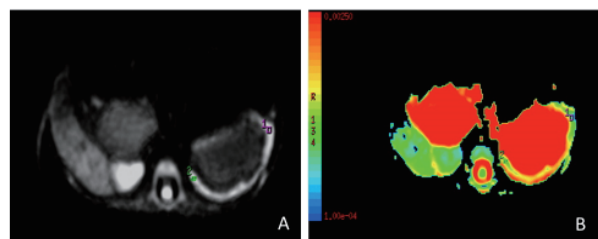


Figure 4. DWI (A) and ADC (B) map of a 5-month-old female infant with left-side congenital hydronephrosis belonging to uremia group. ROIs are manually delineated.

Table 1. The mean renal ADCs of six groups

Groups	Number of kidney	Mean of ADC values	95% confidence interval	Minimum	Maximum
Control group with normal renal parenchyma	60	1.61 ± 0.06	1.60 - 1.63	1.50	1.78
Contralateral kidney group	46	1.51 ± 0.10*	1.48 - 1.54	1.34	1.77
Renal dysfunction compensated group	9	1.46 ± 0.04*	1.43 - 1.49	1.18	1.53
Renal dysfunction decompensated group	13	1.33 ± 0.04	1.31 - 1.36	1.29	1.42
Renal failure group	21	1.22 ± 0.07	1.19 - 1.23	1.13	1.32
Uremia group	3	1.04 ± 0.03	0.97 - 1.12	1.01	1.07

*There was no statistically significance in ADC values between the contralateral kidney group and renal dysfunction compensated group. (*p* = 0.06).

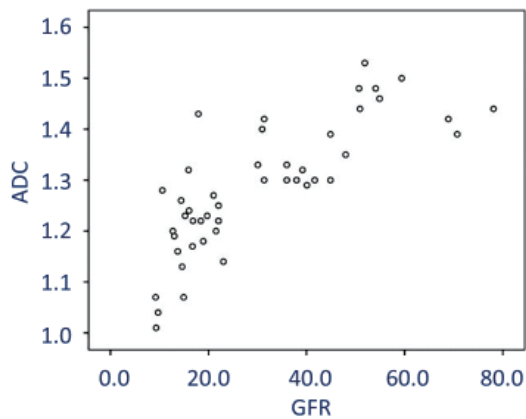


Figure 5. Relationship between ADC values of obstructed kidney with hydronephrosis and the split renal GFR. There was a moderate positive correlation ($r = 0.744, p < 0.001$).

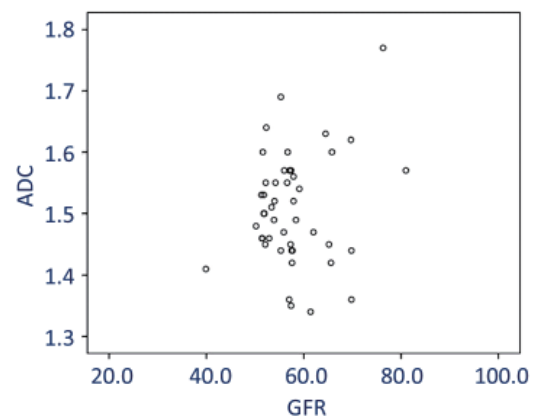


Figure 6. Relationship between ADC values of contralateral kidney with no hydronephrosis and the split renal GFR. There was no a correlation ($r = 0.194, p < 0.001$).

When compared between each two groups, we observe that there was no significant difference of ADCs between renal dysfunction compensated group and contralateral kidney group ($p = 0.06$) and in the rest groups, significant difference was seen between each other ($p < 0.001$).

There was a moderate positive correlation between renal ADCs of the obstructed kidney with hydronephrosis and split renal GFR ($r = 0.744, p < 0.001$) (Figure 5).

No correlation was found between renal ADC values of the contralateral kidneys and split renal GFR ($r = 0.194, p < 0.001$) (Figure 6). The GFR range was 38.9-78 mL/min in contralateral kidney group and 2 out of 46 kidneys in this group was ≤ 50 mL/min.

4. Discussion

4.1. The change pattern of ADC values in hydronephrotic kidneys and the correlation with GFR

The accurate evaluation of renal function to hydronephrotic patients is essential for the diagnosis and treatment of this disease. The surgical operation timing relies on the location and degree of urinary obstruction, as well as the concise assessment of renal function and to what extent the renal function can be recovered after operation (17,18). Hydronephrosis will slow down the transportation of water, reduce transporting volume and restrict molecule movement. Meanwhile, the renal perfusion is reduced as well owing to the increased pressure in renal pelvis and calyces, as well as the collective effects of various cell and vasoactive factors on the renal blood supply. The pathophysiologic changes described above would certainly affect the diffusion in renal parenchyma and alter the ADCs. Our study showed that the ADCs of obstructed kidneys in infants with congenital hydronephrosis were lower than that of normal kidneys ($1.61 \pm 0.05 \times 10^{-3} \text{ mm}^2/\text{s}$), and the difference was significant, which conformed to the previous research results. Several animal experiments and clinical studies in adult (7,19) have shown that the

ADCs dropped in hydronephrosis, and values of ADCs in hydronephrotic kidneys with impaired renal function were much lower than that of the contralateral kidneys with normal renal function (9,13,20). In patients with renal failure, the ADCs of cortex and medulla fell down in varying degree (7,21,22).

In acute phase of hydronephrosis, the interface between cortex and medulla is still visible. However, this differentiation would be no longer clear in chronic urinary tract obstruction (23). Fukuda *et al.* (8) had stated that there is a low signal-to-noise ratio in the kidney images with EPI sequences. As such, it would be difficult to exactly differentiate renal cortex and medulla in that situation and the measurement error will certainly increase when the ROIs are placed onto the cortex and medulla respectively. In addition, Xu *et al.* (11) reported no significant signal difference was found between the renal cortex and medulla in DWI. Therefore, the approach of placing the ROI on specific plane was adopted in this study to measure the ADCs of local renal parenchyma.

Our study indicated that there were significant differences in ADC values between each of four groups, including renal dysfunction compensated group ($1.46 \pm 0.04 \times 10^{-3} \text{ mm}^2/\text{s}$), renal dysfunction decompensated group ($1.33 \pm 0.04 \times 10^{-3} \text{ mm}^2/\text{s}$), renal failure group ($1.22 \pm 0.07 \times 10^{-3} \text{ mm}^2/\text{s}$) and uremia group ($1.04 \pm 0.03 \times 10^{-3} \text{ mm}^2/\text{s}$). The ADC values in renal dysfunction compensated group were lower than that of contralateral kidney group, and significant difference of ADCs was observed between renal failure group and uremia group. Xu *et al.* (12), however, had reported that there was no significant difference of renal ADCs between moderate and severe renal function injury groups when they investigated the healthy people and patients with chronic kidney disease. The authors believed that the reason may be attributed to the small sample in severe renal function injury group. In addition, the criteria they adopted for moderate renal function injury group is different from the renal failure group in our study

($10 \text{ mL/min} \leq \text{GFR} < 20 \text{ mL/min}$ versus $10 \text{ mL/min} \leq \text{GFR} < 25 \text{ mL/min}$), which may lead to the differential conclusion.

The research by Thoeny *et al.* (8) in healthy volunteers demonstrated that DW MRI had a fairly good repeatability in evaluating the changes of renal function, and thus can be performed as a non-invasive follow-up approach to monitor the degree and changes of abnormal renal function. But more research with larger sample size may be required to confirm this observation.

4.2. The change pattern of ADC values in contralateral kidneys and the correlation with GFR

Harriet *et al.* (13) found there was various degree of difference of ADCs between the involved kidney and contralateral kidney in patients with urinary tract obstruction. Our research results showed that the renal ADC values of hydronephrotic kidneys in renal dysfunction compensated group were lower than that of contralateral kidneys but with no significant difference, while the renal ADCs in both groups were lower than that of normal control group. Base on the grouping criteria of renal insufficiency, the GFR of renal dysfunction compensated group is reduced but above 50 mL/min , so the ADCs were lower than that of normal kidneys. Given the fact that no structural lesion is observed in contralateral kidneys, and the partial contralateral kidneys after obstruction would present some level of functional compensation, the renal ADC values of involved kidney in renal dysfunction compensated group were lower than that of contralateral kidneys. In our study, the insignificant difference of ADCs between involved kidney and contralateral kidney may result from the insignificant difference of GFR between them. In addition, in two out of 46 contralateral kidneys, the GFR level is from $25\text{-}50 \text{ mL/min}$. Therefore, a larger sample might be required in future research to confirm the appropriateness of using contralateral kidney as the normal control group in the past researches. Toyoshima *et al.* (9) also believed that there were overlapping of the renal ADCs between hydronephrotic kidneys without renal injury ($1.63 \pm 0.12 \times 10^{-3} \text{ mm}^2/\text{s}$) and the contralateral kidneys with no hydronephrosis ($1.68 \pm 0.15 \times 10^{-3} \text{ mm}^2/\text{s}$). Müller *et al.* (2) found that the contralateral renal ADCs increased only slightly after urinary tract obstruction on one side.

Our study found that the renal ADC values in contralateral kidney group with no hydronephrosis were lower than that of normal kidney control group ($1.61 \pm 0.05 \times 10^{-3} \text{ mm}^2/\text{s}$), and no correlation with split renal GFR was found. In the research of adult hydronephrosis, whereas Toyoshima *et al.* (9) found that the renal ADCs of contralateral kidney without hydronephrosis were similar to that of normal kidney with no correlation with the split renal GFR. In our

study, the range of contralateral renal GFR was $38.9\text{-}79 \text{ mL/min}$. Two out of 46 cases had mild renal function damage ($\text{GFR} \leq 50 \text{ mL/min}$) without renal compensated hyperfunction. Some researchers have indicated that renal compensated hyperfunction in contralateral kidney can occur at early stage of hydronephrosis, but part of renal function was reduced at variable degree after 6-8 months from the occurrence of obstruction. However, the reason of no correlation between the renal ADC values of obstruction contralateral kidney without hydronephrosis and the single renal GFR is still to be further investigated.

4.3. Limitations of the study

Our study has several limits. (i) The number of hydronephrosis cases in uremic group was relatively small; (ii) There is still no accurate interpretation regarding no correlation between the ADCs of contralateral kidneys and split renal GFR; (iii) In order to investigate the relationship thoroughly between the renal ADC values of hydronephrotic kidneys and the split renal GFR, patient grouping with a broader range of age may be required; (iv) Only the ADC values of whole renal parenchyma was measured in this investigation, while we expect to be able to measure the renal cortex and medulla respectively in future research; (v) As GFR is an important index to evaluate the renal filtration function, we expect to investigate the relationship further between the renal ADC values and renal tubular function of split kidney; And as a functional measurement approach, there is a need to further investigate whether the DW MRI could reflect the functional changes in early stage lesions.

In sum, this study revealed that the renal ADC values of involved kidney in infants with congenital hydronephrosis were lower than that of the normal renal parenchyma, and there was a positive correlation between the ADC values of hydronephrotic kidneys and split renal GFR, which may indicate that ADC values are of certain value to evaluate the filtration function of hydronephrotic kidney, and may provide new direction to help clinical physician to find noninvasive novel approach to evaluate the single renal function.

Although the clinical application of renal DWI is to be investigated in depth, the MRI approach shows many advantages in evaluating renal function. For instance, it is non-invasive with no radiation. The combination of conventional MR imaging and DWI can provide the information of kidney morphology and function simultaneously. As DWI does not need using contrast medium, it won't bring any adverse reactions associated with radiation or contrast medium damage to the children during their development and growth period and thus is especially beneficial to the infant patients with allergy to contrast medium and/or impaired renal function. There is a reason to believe

that functional MRI will certainly demonstrate great prospects of clinical application in evaluating renal function in the future, and will play a more important role in the diagnosis of infants hydronephrosis.

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