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Association of Renal Function (Estimate Glomerular Filtration Rate) with the Number of Febrile Urinary Tract Infections in Children with Neurogenic Bladder

Guanglun Zhou[1,*] Man Jiang[2,*] Wenbin Zhu[1] Xiaodong Liu[1] Junjie Sun[1] Shoulin Li[1]

[1] Department of Urology and Laboratory of Pelvic Floor Muscle Function, Shenzhen Children's Hospital, Futian District, Shenzhen, Guangdong, China
[2] Department of Infectious Diseases, Department of Urology and Laboratory of Pelvic Floor Muscle Function, and Department of Clinical Laboratory, Shenzhen Children's Hospital, Shenzhen, China

Address for correspondence Shoulin Li, MD, Department of Urology and Laboratory of Pelvic Floor Muscle Function, Shenzhen Children's Hospital, Futian District, Shenzhen, 518000, Guangdong, China (e-mail: szetyyzyt@163.com).

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Abstract

Introduction Our objective was to evaluate whether renal function, assessed as the estimated glomerular filtration rate (eGFR), is associated with the number of febrile urinary tract infections (FUTIs) in children diagnosed with neurogenic bladder (NB).

Materials and Methods Clinical information of patients diagnosed with NB was prospectively collected between January 2013 and January 2022. Episodes of FUTI were recorded during the follow-up period, and the eGFR was calculated based on the serum cystatin C level. Grading (G1–G5) of chronic kidney disease (CKD) was conducted as described by the eGFR.

Results In total, 463 children were included in the final analysis (265 males and 198 females; mean age: 23 months). The median follow-up time was 51 months. A total of 302 children had four or more FUTIs and 161 children had none to three FUTIs. The incidence of developing CKD G3 to G5 gradually increased from the first to third (1.3–2.4%) episodes of FUTI and drastically increased after four episodes ($\geq$ 22.5%), with the incidence recorded to be 100% after eight FUTIs. The odds of CKD G3 to G5 in children with four FUTIs were 17.3 and 43.7 times greater after four and six FUTIs, respectively, than in children with one FUTI.

Conclusion This study showed that recurrent FUTIs are common in children with NB and that the risk of rapid progression to CKD G3 to G5 increases substantially after four or more FUTIs episodes.

Keywords
- renal function
- glomerular filtration rate
- urinary tract infection
- neurogenic bladder

Introduction

A neurogenic bladder (NB) is a dysfunctional urinary bladder caused by diseases of the peripheral or central nervous system involved in the control of micturition.[1] Additionally, in children with NB other conditions such as recurrent urinary tract infections (UTIs) and vesicoureteral reflux (VUR) may lead to kidney scarring and failure.[2] Nseyo and Santiago-Lastra reported that febrile urinary tract infections (FUTIs) are related to the risk of renal damage.[3] Shaikh et al

* *These authors contributed equally and retain the first authorship.*

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found that renal scarring is an important sequela of FUTIs in children and that each new FUTI incident increases the risk of kidney scarring by 2.8, 25.7, and up to 28.6% after the first, second, and third or more FUTI incident, respectively.[4]

Although dimercaptosuccinic acid (DMSA) detection of renal scarring is an important indicator of renal function, the glomerular filtration rate (GFR) is accepted as the best overall indicator of renal function.[5] In addition, the use of a DMSA scan in clinical practice is limited.[6] Moreover, the relationship between the number and size of renal scars relative to renal function remains unclear. In contrast, serum cystatin C (Cys-C) is an endogenous marker used for estimated GFR (eGFR) and Cys-C levels are independent of muscle mass and age.[7] The Cys-C-based equations are an accurate method for renal function evaluation in children with NB.[7] In our clinical practice, we also found that Cys-C-based equations are a more precise method for renal function evaluation in juvenile patients than serum creatinine. Thus, understanding the relationship between the number of episodes of FUTI and changes in eGFR (Cys-C-based equations) is necessary.

This prospective study aimed to examine the association between the number of episodes of FUTIs and changes in eGFR.

Materials and Methods

This study collected the clinical information of patients diagnosed with NB from January 2013 to January 2022 at our institution. Inclusion criteria were as follows: (1) NB, which was attributed to congenital neurological diseases, first diagnosed at our institution, (2) the follow-up time of over 12 months after diagnosis; (3) eGFR $\geq$ 90 mL/min/1.73 m^2 was confirmed when NB was diagnosed. The exclusion criteria were patients with thyroid or adrenal cortex dysfunction or patients that were wheelchair bound or paralyzed. The congenital neurological diseases attributed to NB comprised 308, 196, and 1 case(s) of myelomeningocele, spina bifida, and meningocele, respectively. For each patient with an initial diagnosis of NB, a comprehensive examination should be performed, including blood biochemistry (serum creatinine, serum Cys-C, etc.), urinary tract ultrasound, urodynamic study, and voiding cystourethrography. The presence or grading of VUR was based on voiding cystourethrography, according to international standards. Detrusor overactivity was recorded as "absent" or "present." Information including age at diagnosis of NB, serum creatinine, serum Cys-C, and VURwase collected. The eGFR was calculated based on the serum Cys-C levels using the chronic kidney disease (CKD) in children equation.[8] Informed consent was obtained from the parents or guardians of all patients prior to examination/treatment, and participants did not receive a stipend. This prospective study was approved by the Institutional Review Board of our hospital.

The management plan was formulated according to the results of urodynamics for each patient with NB. Intermittent catheterization should be commenced in children with NB as early as possible. In a small number of children without any clear sign of outlet obstruction, intermittent catheterization could be delayed; however, these children require close follow-up. Anticholinergic medication was used to treat detrusor overactivity. If VUR is present, prophylactic antibiotics should be started when patients experience recurrent UTIs. Patients with NB were followed-up and examined according to the recommendations of the European Association of Urology Guidelines on Pediatric Urology. In this study, FUTI episodes were recorded during the follow-up period. The FUTI was defined as the presence of a recorded temperature more than 38°C within 24 hours of diagnosis of UTI, pyuria on urinalysis, and 50,000 colony forming units/milliliter or more of a single organism on culture from a specimen obtained via catheterization.[4] Routine examinations (including serum creatinine, serum Cys-C, etc.) were performed within 3 months of the FUTI episode to assess renal function (eGFR). During the study period, the follow-up was terminated if the children required urologic surgery, dialysis, or renal transplant. However, the medical records of these patients were recorded in detail to document episodes of FUTIs during the study period and included in this final study analysis. At the end of this study, Cys-C and serum creatinine levels that were not measured within 3 months of the most recent FUTI during follow-up were excluded from the final analysis. Patients with missing data were defined as those included in the study but lacking the data required for final statistical analysis.

Grading of CKD was conducted as described by eGFR[9] (G1: $\geq$ 90 mL/min/1.73 m^2, G2: 60–89 mL/min/1.73 m^2, G3: 30–59 mL/min/1.73 m^2; G4: 15–29 mL/min/1.73 m^2, G5: $<$ 15 mL/min/1.73 m^2). A decreased eGFR was defined as G1 upgrading to G2 to G5.

Statistics

Continuous variables are presented as mean standard deviation; categorical variables are presented as frequencies and percentages (%). Statistical analysis was performed using SPSS version 25.0, and statistical significance was set at *p*-value less than 0.05.

Results

A total of 505 children were enrolled in this study, of which 42 were excluded due to missing data. Thus, a total of 463 children were included in the final analysis. Of these patients, 140 had VUR and 323 had no VUR. The mean initial age at diagnosis of NB was 23 months (range, 9–74 months). The median follow-up was 51 months (range, 12–97 months). A total of 18, 31, 43, 69, 80, 76, 82, 60, and 4 patients had no, 1, 2, 3, 4, 5, 6, 7, and 8 FUTI episodes, respectively. The average hospital stay for an FUTI episode was 18.5 days (range 9–25 days).

The incidence of decreased eGFR was 5.6% (1/18, CKD G2) for patients with no FUTI, 6.3% (28/445, 22 with CKD G2 and 6 with CKD G3) after one FUTI, 7.2% (30/414, 24 with CKD G2 and 6 with CKD G3) after two FUTIs, 9.7% (36/371, 27 with CKD G2 and 9 with CKD G3) after three FUTIs, 29.8% (90/302, 22 with CKD G2, 66 with CKD G3 and 2 with CKD G4) after four FUTIs, 36.5% (81/222, 12 with CKD G2, 67 with CKD G3

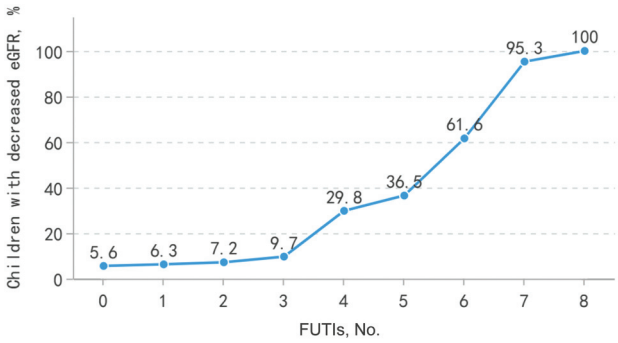

Fig. 1 Incidence of acquired decreased eGFR according to the number of episodes of febrile urinary tract infections. eGFR, estimated glomerular filtration rate.

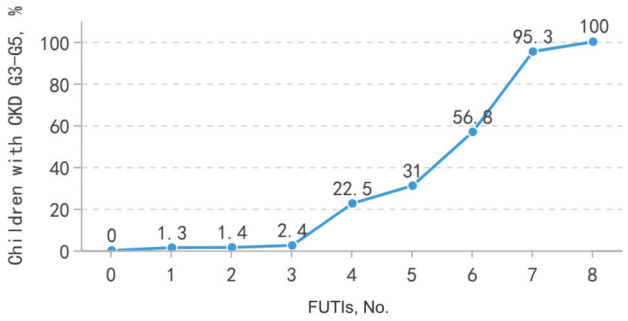

Fig. 2 Incidence of develop to CKD G3 to G5 according to the number of episodes of febrile urinary tract infections.

and 2 with CKD G4) after five FUTIs, 61.6% (90/146, 7 with CKD G2, 80 with CKD G3 and 3 with CKD G4) after six FUTIs, 95.3% (61/64, 59 with CKD G3 and 2 with CKD G4) after seven FUTIs, and 100% (4/4, 3 with CKD G3 and 1 with CKD G4) after eight FUTIs (►Fig. 1). The odds of decreased eGFR with four FUTIs were 4.7 times greater than those with one FUTI, and the odds of decreased eGFR with six FUTIs were 9.8 times greater than those with one FUTI.

The incidence of developing CKD G3 to G5 was 0% (0/18) in those with no FUTI, 1.3% (6/445) after one febrile UTI, 1.4% (6/414) after two FUTIs, 2.4% (9/371) after three FUTIs, 22.5% (68/302) after four FUTIs, 31.0% (69/222) after five FUTIs, 56.8% (83/146) after six FUTIs, 95.3% (61/64) after seven FUTIs, and 100% (4/4) after eight FUTIs (►Fig. 2). The odds of CKD G3-G5 with four FUTIs were 17.3 times greater than those with one FUTI, and the odds of CKD G3-G5 with six FUTIs were 43.7 times greater than those with one FUTI.

In the VUR group, 109 children had four or more FUTIs and 31 children had 0 to 3 FUTIs. In the non-VUR group, 193 children had four or more FUTIs and 130 children had none to three FUTIs. There was a statistically significant difference in the frequency of four or more FUTIs between the two groups ($p < 0.05$).

In the detrusor overactivity group, 191 children had four or more FUTIs and 78 children had no to three FUTIs. In the nondetrusor overactivity group, 111 children had four or more FUTIs and 83 children had no to three FUTIs. There was a statistically significant difference in the frequency of four or more FUTIs between the two groups ($p < 0.05$).

Discussion

The main goals of NB management are the prevention of UTI and deterioration and the promotion of as good quality of life as possible.[10] The risk of renal damage increases substantially with recurrent FUTIs;[6] thus, the prevention of recurrent FUTIs and consequent upper urinary tract deterioration is vital for patients with NB. Our data suggest that the risk of decreased eGFR and progression to CKD G3-G5 increases substantially after four FUTIs. Moreover, patients with VUR are more likely to have recurrent FUTIs than those with no VUR.

Episodes of FUTI are common in children with NB.[3] In this study, 65.2% of patients experienced four or more episodes of FUTIs, further confirming that patients with NB are at the risk of recurrent FUTIs. This could be attributed to certain factors, including poor bladder management leading to chronic bacteriuria, urinary stasis, and VUR.[3] In addition, detrusor sphincter dysfunction persists in most of these children, and urodynamic characteristics may deteriorate over time.[11] Therefore, we believe that with the extension of the follow-up time of patients with NB, the number of FUTI would gradually increase. DeJong et al found that 20% of readmissions were attributed to UTI in patients with spinal cord injuries, with an average hospital stay of 15.5 days and notable health care expenditures.[12] Similarly, our data showed that the average hospital stay for FUTI was up to 18.5 days, which seriously affected the quality of life of these children.

Shaikh et al reported that each new FUTI increases the risk of kidney scarring by demonstrating that a significantly increased risk (25.7%) of kidney scarring after the second FUTI and up to 28.6% after the FUTIs.[4] In this study, the risk of decreased eGFR gradually increased with each new FUTI, and the risk of decreased eGFR increases substantially after four episodes FUTIs. According to the study by Shaikh et al,[4] when the number of FUTIs is less than four, many NB patients may develop renal scars; however, the present study showed that the eGFR of most children was still within the normal range. Moreover, the subjects in the study by Shaikh et al were children with non-NB with no long-term follow-up and data comprising four or more FUTIs.[4] Our data suggest that the incidence of decreased eGFR after the four FUTIs was 29.8 and 61.6% after the six episodes and up to 100% after eight FUTIs. This may be due to multiple FUTIs causing widespread renal structural damage, further causing a decrease in GFR. This study showed that the risk of decreased eGFR increases rapidly after four or more episodes of FUTIs.

With the decline in eGFR, many complications arise, including loss of renal exocrine or endocrine function, manifesting as conditions such as acidosis, malnutrition, anemia, and mineral and bone disorders.[9] A meta-analysis showed associations of eGFR less than 60 mL/min/1.73 m^2 with a subsequent risk of cardiovascular and all-cause mortality, CKD progression, and kidney failure in the general population.[9,13] In our study, when children had four FUTIs, the risk of progression to CKD G3 to G5 (eGFR < 60 mL/min/1.73 m^2) was significantly increased. The incidence of developing CKD

G3 to G5 after the four FUTI episodes was 22.5 and 56.8% after the six FUTIs and up to 100% after eight FUTIs. Similarly, Bush et al reported that new kidney injury only occurs in patients with recurrent FUTIs.[6] Therefore, we believe that reducing the risk of FUTI recurrence can prevent the risk of further renal damage.

A diagnosis of VUR is a common finding in NB, which is usually secondary to bladder dysfunction[14] and does not commonly resolve with age.[15] In the present study, children with NB complicated by VUR were more likely to develop subsequent episodes of FUTIs, indicating an increased risk for recurrent FUTIs from a potentially correctable anomaly. Hum et al found VUR to be a significant risk factor for recurrent FUTIs.[16] Moreover, detrusor overactivity is associated with the risk of recurrent FUTI in children with NB. Similarly, Seki et al reported detrusor overactivity to be an independent factor in the incidence of FUTI in patients with myelodysplasia.[11]

This study has some limitations. First, the GFR was assessed using Cys-C instead of inulin clearance. Although renal clearance of inulin remains the gold standard for eGFR at present, it is an expensive and time-consuming method, which can also lead to severe allergic reactions.[17,18] Second, some potential confounding factors may have affected renal function.

Conclusion

This study showed that recurrent FUTIs are common in children with NB. The risk of decreased eGFR gradually increased with each new episode of FUTI and increased substantially after four episodes of FUTIs. Similarly, the risk of progression to CKD G3 to G5 significantly increased in patients with four or more episodes of FUTI.

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Conflict of Interest

None declared.

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