

Acute focal bacterial nephritis with vesicoureteral reflux in infants

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Abstract

Background

Acute focal bacterial nephritis (AFBN) is a seldom infection in children kidney disease, Vesicoureteral reflux (VUR) often exist in infants who are easy to have urinary tract infection (UTI). In this study, we summarize the clinical features, imaging and therapy.

Methods

eleven patients with AFBN and VUR aged from two months to eight months treated at this hospital from January 2017 to August 2019 were reviewed. The manifestations, urine and blood tests, imagings, treatments of patients were analyzed retrospectively.

Results

Fever was the common symptom, blood CRP was higher than normal (25 mg/L-200 mg/L), The percentage of neutrophils in blood was 52%-85%. The ratio of neutrophils to lymphocytes was 1.39-11.6, Routine urine microscopic examination of leukocyte was +~3+/HP, Urine culture samples were 42, 34 samples were positive, the positive rate was 80.95%. Diagnosis was set by CT combined MCU. Enhanced CT conducted for all patients showed hypoperfused wedged-shaped or round and space-occupying lesions in kidney. MCU conducted showed I-V grade VUR in single or both sides. 9 cases were treated with prophylactic antibiotics, DxHA injection was operated on 1 case, cohen operation for another patient. Relapses were rarely occur after insisting on treatment.

Conclusion

AFBN in children are rare and associated with VUR. Patients with AFBN should perform MCU to find out VUR and insist on prophylactic antibiotic until the VUR disappeared, patients with recurrent infection and serious VUR need urological treatment in order to prevent the formation of renal scar.

Background

Urinary tract infection includes upper urinary tract infection (UUTI) and lower urinary tract infection (LUTI) according to the location infected, the treatment and prognosis of UUTI and LUTI are quite different. AFBN is a kind of serious UUTI, and even worse than acute pyelonephritis (APN), The patients who have AFBN are almost infants and young children, AFBN can lead to renal scar and secondary hypertension, chronic renal failure. Vesicoureteral reflux (VUR) includes primary VUR and secondary VUR. Primary VUR is one of the pathogenic factors of AFBN and often exists in infancy stage [1]. In this paper, we analyzed the clinical

data of 11 infants cases with AFBN and VUR diagnosed and treated in our hospital in recent years retrospectively to improve the understanding of the two diseases.

Methods

Patients data Eleven infants with AFBN combined with VUR at Tianjin Children's Hospital from January 2017 to August 2019 were reported here. Table 1 shows the age, sex, symptom, urine culture and blood test and so on. There are 5 males and 6 females in this study, and the age is from 2 to 8 months, the median age is 5 months. The diagnostic criteria of AFBN were based on the results of renal computed tomography (CT) performed with contrast medium. The VUR diagnostic criteria is according to the five grades classification proposed by the international association of reflux nephropathy. The gold standard diagnosis is micturating cystourethrography (MCU), and the other urinary malformation diseases were excluded.

Clinical data and laboratory analysis the pathogenesis characteristics, family history and clinical manifestations of eleven infants were collected. Laboratory examination included urine routine, urine culture, C-reactive protein (CRP), blood neutrophil percentage (BNP), neutrophil-to-lymphocyte ratio (NLR).

Imaging examination methods: FHILPS Epiq5 color ultrasonic diagnostic instrument was used. CT examination used philips 256-row iCT scanner, followed by a three-phase dynamic enhanced scan, and iodine contrast medium was given at 1.5 ml/kg, arterial, venous and delayed scanning were followed after injection. SIMENS luminous select was used for MCU examination. After inserting the urine tube from the urethral orifice to the bladder, inject 76% meglumine diatrizoate contrast medium 40–80 ml by 1:4 according to the age, and then observe the reflux at bladder filling period and urination period.

Ethics

This study was approved by the medical ethics committee of Tianjin Children's hospital. All the guardians of the children gave consent to the study and signed informed consent.

Results

Clinical manifestations every patient had a fever, poor appetite, and had not irritative voiding symptoms, lethargy, vomiting, diarrhea or constipation. There was no family history of urinary malformation in 11 cases. (Table 1)

Laboratory examination Table 1 shows that all urine routine tests were leukocyte urine, leucocyte count were from +/HP to 3+/HP. 42 Urine culture were done and 34 samples were positive. The bacterial colony count was $> 10^5$ /mL, the positive rate was 80.95%. There were 19 gram-negative bacterias, 7 cases were *Escherichia coli*, 10 cases were *Pseudomonas aeruginosa*, 1 case was *Klebsiella pneumoniae* and 1 case was *Acinetobacter baumannii*. There were 15 gram-positive bacterias, 11 cases were *Staphylococcus faecium*, 3 cases were *Enterococcus faecalis* and 1 case was *Enterococcus gallinarum*. Blood CRP was from 25 mg/L to

200 mg/L. The percentage of neutrophils in blood was 52%-85%. The ratio of neutrophils to lymphocytes was 1.39–11.6. No abnormalities were found in the blood renal function tests, and all blood cultures were negative.

Imagign examination There were 4 infants infected in single kidney (3 infants in left and 1 in right) and 7 infants infected in both kidneys; 10 infants had left VUR (1 case of grade I, 2 cases of grade II, 2 cases of grade III, 3 cases of grade IV and 2 cases of grade V). 9 infants had right VUR (4 cases of grade II, 2 cases of grade III, 1 case of grade IV, 2 cases of grade V). results of 10 cases showed abnormalities in the first b-ultrasound examination, which showed different degrees of renal pelvis dilation, ureter dilatation and hydronephrosis. CT scan and enhancement of the kidney showed that the lesion was in different degrees of decreased wedge perfusion. MCU showed unilateral or bilateral VUR and the grade was from I to V (Table 2, Fig. 1, 2, 3, 4)

Therapy and follow-up Before any antibiotic therapy was started, urine specimen should be obtained for urine culture. Antibiotic treatment is emergency to eradicate the infection. Antibiotic was given for 10–14 days according to the drug susceptible test, when MCU examination showed VUR, followed by daily low dose antibiotics taken at night. MCU examination was arranged after infection controlled within 2–4 weeks. Only 3 infants' parents agreed to MCU examination and insisted on antibiotic prophylaxis at the first infection. Febrile UTI was repeated 1–3 times in other 8 cases within the follow 4–9 months. Then they had the MCU examination which showed VUR, and insisted on antibiotic prophylaxis. Two infants haven't recurrent infection since we followed up for 3–5 months long. The other 9 infants were followed up for 11–39 months, and 7 infants stopped the daily low dose antibiotics by themselves, then they had the febrile urinary tract infection 1–3 times. Two patients still had febrile urinary tract infection during the daily low dose antibiotics therapy and were transferred to surgical correction, one infant had Cohen operation, and another infant had the dextranomer/hyaluronic acid (DxHA) injection treatment. No recurrent infection occurred after surgical treatment. (Table 1)

Table 1
Clinical data of 11 children with APN combined with VUR

Case	Fever	CRP mg/L	BNP	NLR	Follow-up duration	UTI times	Pathogenic bacteria	Treatment options
1	+	106	0.52	1.39	39 ms	4	Escherichia coli Faecium	Antibiotic prophylaxis
2	+	42	0.62	2.13	37 ms	2	Enterococcus faecalis	Antibiotic prophylaxis
3	+	25	0.71	2.83	11 ms	3	Escherichia coli Faecium	Antibiotic prophylaxis
4	+	129	0.85	10.24	33 ms	4	Enterococcus faecalis Faecium Pseudomonas aeruginosa Klebsiella pneumoniae	Antibiotic prophylaxis
5	+	85	0.85	10.12	32 ms	4	Escherichia coli Faecium Acinetobacter baumannii Enterococcus gallinarum	Antibiotic prophylaxis
6	+	200	0.75	3.61	31 ms	3	Faecium Pseudomonas aeruginosa	Antibiotic prophylaxis
7	+	96	0.83	8.31	28 ms	5	Pseudomonas aeruginosa	Cohen operation
8	+	80	0.76	4.21	35 ms	4	Escherichia coli Faecium	DxHA Injection
9	+	159	0.85	11.6	27 ms	4	Faecium	Antibiotic prophylaxis
10	+	38	0.72	3.66	5 ms	1	Enterococcus faecalis	Antibiotic prophylaxis
11	+	56	0.56	1.45	3 ms	1	Escherichia coli	Antibiotic prophylaxis

M,month;M,male;F,female

Table 2
imaging of AFBN combined with VUR

case	B-ultrasonography	Enhanced CT	MCU: VUR grade
1	Right hydronephrosis with dilatation of ureter	Wedge-shaped areas of decreased nephrogenic density in right renal	L:no R:III
2	The right kidney was 58 × 29 mm, and the left kidney was 55 × 18 mm	Wedge-shaped areas of decreased nephrogenic density in both renals, ureter dilated hydronephrosis in both sides	L:IV R:IV
3	Left pyelectasis ,6 mm	Multiple decreased perfusion areas in left renal parenchyma(<i>Fig. 1A,1B</i>)	L:IV R:II (<i>Fig. 1C</i>)
4	Right pyelectasis,12 mm Left pyelectasis, 9 mm	Multiple decreased perfusion areas in both renal parenchyma (<i>Fig. 2A,2B</i>)	L:I R:III (<i>Fig. 2C</i>)
5	pyelectasis and dilatation of ureter in both sides	Wedge-shaped areas of decreased nephrogenic density in both renals	L:III R:II
6	hydronephrosis and dilatation of ureter in both sides	Multiple decreased perfusion areas in both renal parenchyma (<i>Fig. 3A</i>)	L:V R:V (<i>Fig. 3C</i>)
7	hydronephrosis and dilatation of ureter in right side	Multiple decreased perfusion in bilateral parenchyma	L: IV R: V
8	localized uneven low echo area in the right upper middle segment of the right kidney	The right kidney shape is irregular, The lower perfusion area in the upper parenchyma of both kidneys. (<i>Fig. 4A</i>)	L:II R:II (<i>Fig. 4B,4C</i>)
9	mild hydronephrosis in both kidneys	Wedge-shaped areas of decreased nephrogenic density in left renal.	L:III R:no
10	Hydronephrosis in both kidneys and overall dilatation of ureter in two sides	Wedge-shaped areas of decreased nephrogenic density in both renals	L:V R:no
11	No abnormalities were observed in both kidneys	Wedge-shaped areas of decreased nephrogenic density in left renals	L:II R:II

Discussion

VUR was first observed by Pozzi in 1893, and Kretschmer had discovered the relationship between VUR and UTI from 1916 to 1929. Tse believed that VUR was caused by abnormal bladder function and insufficient ureter length in the bladder wall, while Alexander believed that VUR was mainly caused by abnormal bladder function, and Alsowayan confirmed this theory through urodynamics research.[2, 3, 4] Primary VUR maybe relieved and disappear according to the age. MCU is the gold standard for the diagnosis and grading of VUR. AFBN belongs to the UUTI, refers to acute suppurative inflammation caused by various pathogenic microorganisms invading the renal pelvis, calyces and renal parenchyma. Most pathogenic microorganism are bacteria, and the most bacteria is Escherichia coli. At present, the gold standard for the localization and diagnosis of urinary tract infection is ⁹⁹Tc-DSMA. Some researchers report that AFBN happens at any age stages, but the incidence of infants is higher than others, 30% infants from 6 to 12 months with AFBN would recurrent after the first infection[5]. The younger they are, the higher danger of recurrence is. VUR is the first reason for AFBN recurrence, the other reasons include bladder and bowel dysfunction (BBD), age, race, etc. When VUR and BBD exist at the same time, the risk is higher [6]. In this study every patient is less than 1 year old, which was consistent with literature reports. There was not defecation abnormalities or urinary abnormalities family history, it is necessary to increase the sample numbers to observe the relationship between the two factors and AFBN recurrence.

Since AFBN can cause renal scarring, it is necessary to find the presence of VUR or other malformations after the diagnosis of AFBN to determine how to prevent recurrence. Imaging studies are performed for UTI localization, urological malformation, renal scarring, and renal function evaluation. Imaging diagnosis includes B ultrasound, MCU, CT and DMSA[7]. Some studies found that renal enhanced CT examination also has a high specificity and sensitivity for the diagnosis of AFBN [8, 9]. Due to the absence of DMSA instrument in our hospital, 11 infants in this group had renal enhanced CT examination, and the lesion area had multiple wedge-shaped decreased perfusion area. Repeating examination after 3 months showed improvement in the lesion area, The imaging changes support infectious lesions. Due to the dynamic changes of VUR, the sensitivity of b-ultrasound is not high, and the value of finding VUR is limited. But if hydronephrosis or dilatation of ureter found by b-ultrasound, it indicates that the patient perhaps have VUR, which requires further imaging examination. In this paper, 10 of the 11 cases were abnormal in b-ultrasound examination, and further renal enhanced CT was consistent with AFBN imaging changes. Although MCU is the gold standard for the diagnosis and grading for VUR, it is difficult for infants to put catheters into catheters and also increases the risk of UTI, so it is not acceptable easily for parents. Only 2 of the 11 children agreed to the examination within 3 weeks after the first infection, and the other infants' parents agreed to the examination after febrile urinary tract infection repeating for 2-4 times. The results of MCU examination showed that the VUR is I-V grade, and 2 patients showed a reduction in regurgitation at 6-11 months interval after the first MCU examination, while the rest were still in follow-up.

The most infants with AFBN did not complained backache or kidney area taps pain because of the age, if they have a high fever (T 39 ° C or higher), renal ultrasound abnormality, urine bacteria infection except E.coli ities, blood neutrophils ratio > 60% or CRP > 40 mg/L, which are the most possible predictions of

renal scarring[10].A study on 2-month-infant with AFBN and VUR showed that when the VUR grade is III - V, the percentage of peripheral blood neutrophils (BNP),The ratio of neutrophils to lymphocytes (NLR) was significantly higher than that of patients with VUR grade I-III [11].In this study, blood CRP 25 mg/L-200 mg/L,The percentage of neutrophils in blood was 52%-85%.The ratio between neutrophils and lymphocytes was 1.39–11.6, which was consistent with the reported literature.

Renal scarring is one of the causes of chronic renal failure, risk factors of renal scarring include the III-V grade VUR. Febrile UTI keeping on 2 days and the recurrence UTI[12],animal experiments showed that in the first seven days of infection, rapid and effective treatment can prevent renal scarring, early appropriate treatment can reduce the damage of kidney,It is a consensus that choose the antibiotic according to the results of urine culture and drug susceptibility test [13, 14, 15].In patients with recurrent UTI or AFBN caused by VUR, continuous antibiotic prophylaxis can significantly reduce the risk of urinary tract infection, although this therapy can increase the risk of antibiotic bacterial resistance[16].According to a Swedish study antibiotic prophylaxis can effectively prevent the new renal scar formation in patients with III-IV degrees VUR ,but in the observation group of 42 girls without using antibiotic prophylaxis,there was 5 cases appeared new kidney scar, which was confirmed by DMSA scan after 2 years .it means that the prevention and treatment of oral drugs for a long time can stop the end-stage kidney disease progression[17].But other studies have shown that low dose antibiotic prophylaxis in girls with VUR or BBD has good curative effect,which did not reduce the occurrence of febril UTI in patients with III-V grade VUR.The risk in prevention treatment group is even higher than control group, the reason may be associated with antibiotics increased bacterial drug resistance[18]. 9 cases in this article do not have UTI again since they insist on using antibiotic prophylaxis.

Studies showed that DxHA endoscopic injection is a method to solve VUR.The success rate is 79% in II grade, 72% in III grade, 63% in IV grade, 51% in V grade, the success rate is not high and the effect is not lasting.[19, 20]There was no significant difference between endoscopic intradermal injection and antibiotic prophylaxis in reducing urinary tract infection recurrence and renal scar formation, but endoscopic treatment reduced recurrent febrile urinary tract infection.[21]A study of repeating MCU on 18.9% patients who have one or more times febril UTI after surgery found that VUR were still exist in 48.8% patients, then researchers summarized the risk factors in these febril UTI patients recurrence include Cystitis cystitis was present at injection, renal scar existing before surgery, the implant disappeared found by B ultrasonic examination after 3 months follow-up. [22]In this study, only one patient received this treatment in another hospital, and there was no recurrence in 5 months follow-up.An other case had cohen operation because of severe reflux.These two patients did not have the febril UTI when they stop the antibiotic prophylaxis after operation. The prognosis of three kinds treatment is different ,Some scholars reported that the recurrence rate after antibiotic prophylaxis was 12%-36%, the recurrence rate after surgical reimplantation was 4.6–24%, and the recurrence rate after endoscopic treatment was 0.75-27%[23, 24], it suggests that the treatment plan for patients with VUR should be discussed by nephrology and urology doctors.

Conclusion

AFBN in children are rare and associated with VUR. Patients with AFBN should perform MCU to find out VUR and insist on prophylactic antibiotic until the VUR disappeared, patients with recurrent infection and serious VUR need urological treatment in order to prevent the formation of renal scar.

Abbreviations

AFBN: Acute focal bacterial nephritis; VUR: Vesicoureteral reflux; UTI: urinary tract infection; MCU: micturating cystourethrography; CT: computed tomography; UUTI: upper urinary tract infection; LUTI: lower urinary tract infection; CRP: c-reactive protein; BNP: blood neutrophil percentage; NLR: neutrophil-to-lymphocyte ratio; APN: acute pyelonephritis.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The work was approved by the Tianjin Children's Hospital Ethics Committee and informed consent was obtained from all subjects.

Consent for publication

Written informed consent will be taken from all participants before their taking part in the study.

Availability of data and materials

All data generated or analysed during this study are included in this article [symptom, laboratory test data, and so on].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YL is first author who wrote the first draft of the manuscript and contributed to the design of the study; WHW performed the literature research; JC and DL performed the imaging pictures, CQC refined the protocol and the principal investigators of this study; All authors revised the protocol critically for important intellectual content and approved the final manuscript.

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Figures

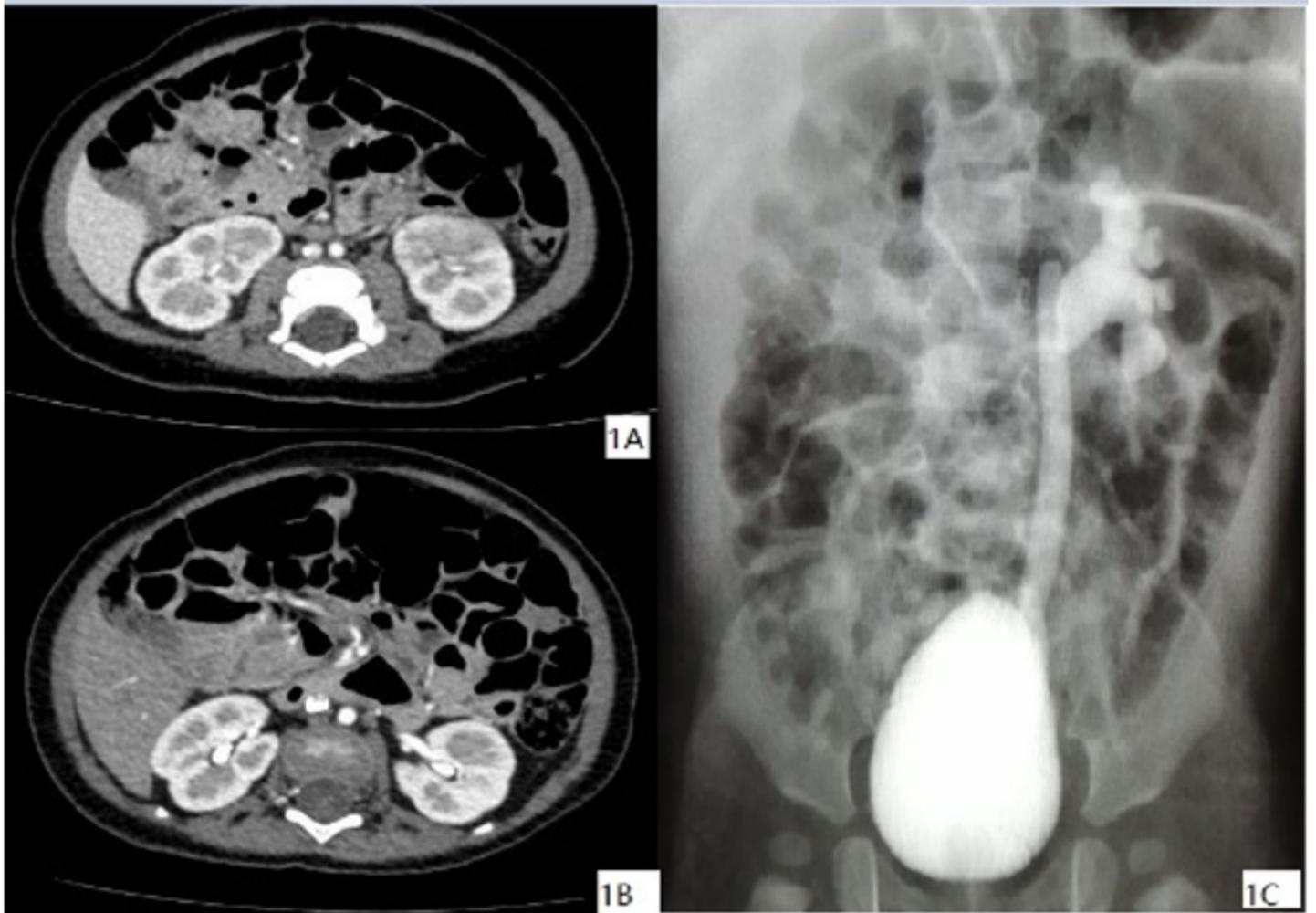


Figure 1

case 3 1A Multiple irregular lamellar hyperfusion areas were observed in the left renal parenchyma and no abnormal density shadow was observed in the right renal parenchyma. 1B After 3 months, multiple irregular lamellar hypoperfusion areas were observed in the left renal parenchyma in CT enhancement and the scope was smaller than before. 1C Contrast medium refluxed from bladder to bilateral ureter and renal pelvis, left ureter, renal pelvis and calyces dilated, right ureter and calyces had not significantly dilated.



Figure 3

case 4 2A CT enhancement showed uneven enhancement of bilateral renal parenchyma, and multiple patches of decreased perfusion were visible. 2B After 3 months repeated the enhanced CT, uneven enhancement of bilateral renal parenchyma was visible, the area is smaller than before. 2C Contrast medium refluxed from bladder to right ureter, pelvis and calyces and left ureter.

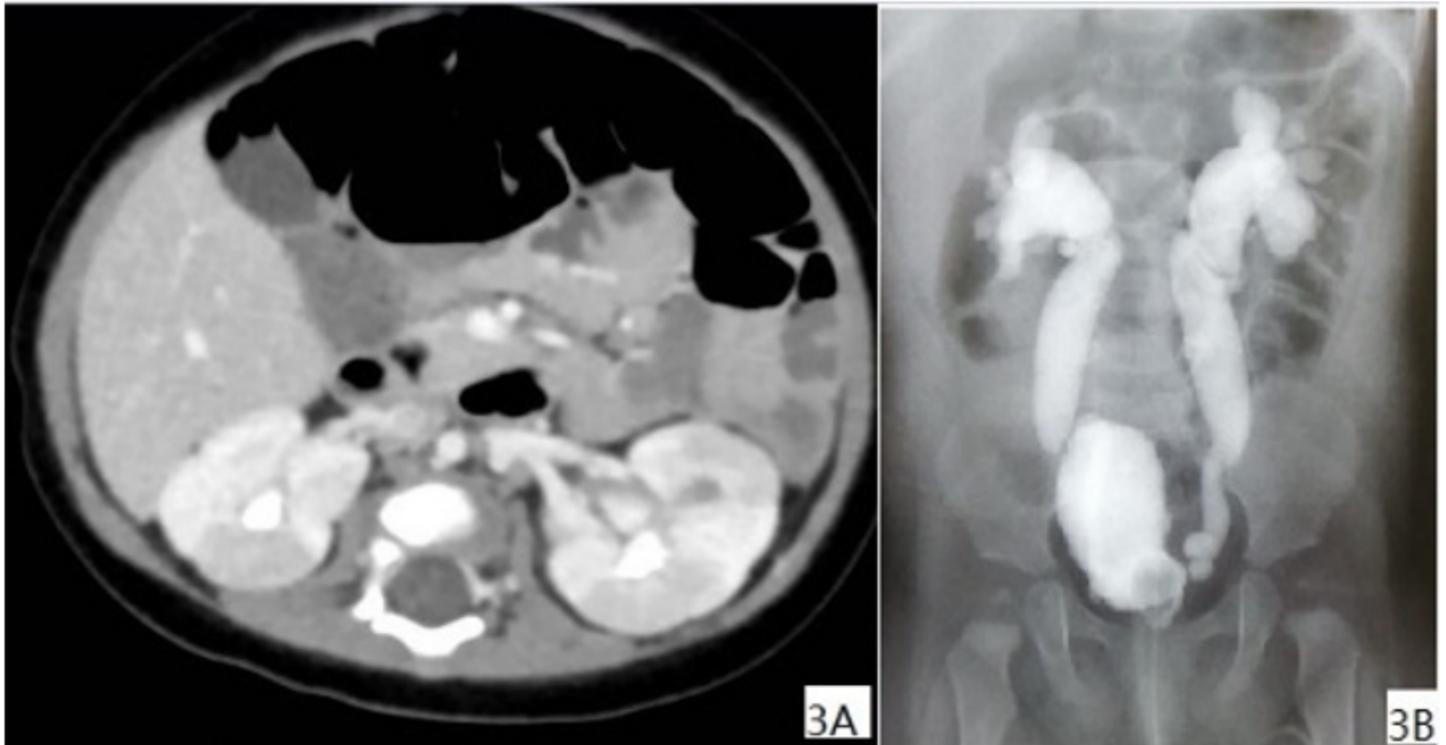


Figure 5

case 6 3A Enhanced CT showed multiple irregular lamellar hypoperfusion areas in the parenchyma of both kidneys, involving the cortex and medulla. 3B Contrast medium refluxed from bladder to bilateral ureter, renal pelvis and calyces, renal pelvis and calyces dilatation.

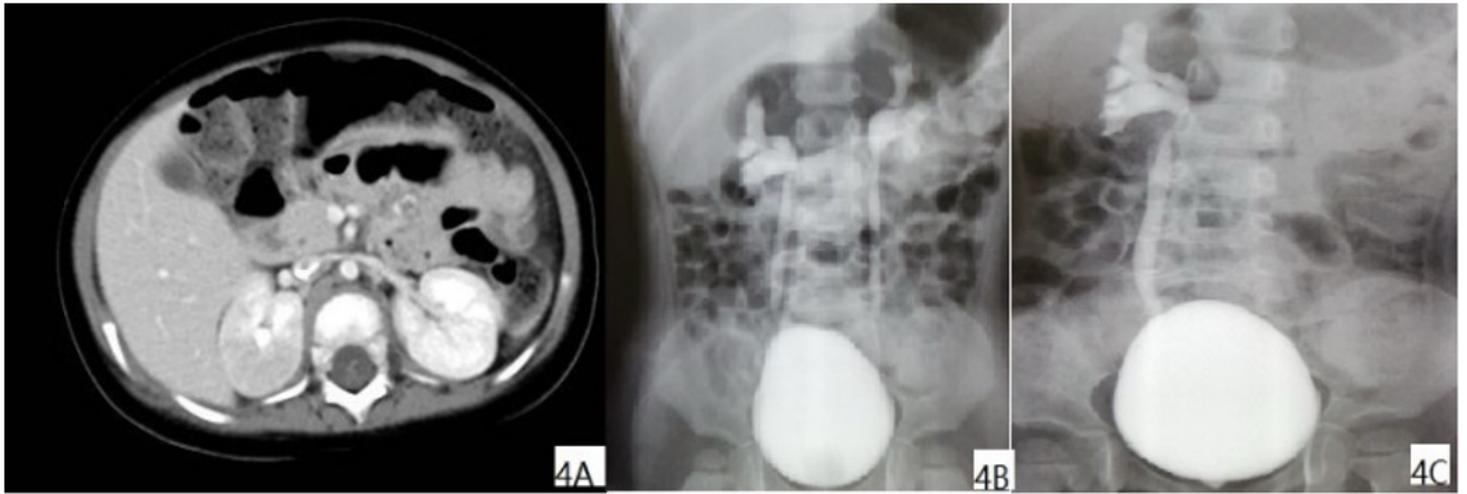


Figure 7

case 8 A Enhanced CT showed irregular patchy and wedge hypoperfusion areas in the upper pole parenchyma of both kidneys, involving both the cortex and medulla, right renal shape is irregular. 4B Contrast medium in the bladder refluxed into both ureters and kidneys, the renal pelvis and calyces were slightly dilated, and ureters were not significantly dilated. 4C After 1 year, repeated the MCUG during urination, contrast-medium flow into the right renal pelvis, the renal pelvis and calyces were slightly dilated, ureter was not dilated, and no reflux was found at the left.