Percutaneous Ultrasound-Guided Renal Biopsy in Children: The Need for Renal Biopsy in Pediatric Patients with Persistent Asymptomatic Microscopic Hematuria

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Background: Percutaneous renal biopsy (PRB) is essential for the diagnosis, prognosis, and management of children with unknown kidney disease. In this study, the safety and efficacy of PRB is investigated, and also the common etiologies of childhood kidney disease, based on histological findings. In addition, we explored the role of PRBs in the diagnosis of children who presented with persistent asymptomatic hematuria.

Methods: By chart review, from July 2005 to July 2009, a total of 99 PRBs were performed on 91 children (43 girls and 48 boys; mean age, 10.9 ± 4.4 years) under ultrasound (US) guidance, by a doctor, using an automated 18-gauge biopsy needle following the same protocol, at a medical center in northern Taiwan.

Results: The accuracy of the histological diagnosis was excellent. The most common post-biopsy complications were perirenal hematoma (11.1%) and asymptomatic gross hematuria (3.0%), respectively. Nevertheless, these complications resolved spontaneously, and none had major bleeding episodes. Histological results showed that lupus nephritis, minimal change disease, and IgA nephropathy (IgAN) could be the current leading causes of childhood kidney diseases in Taiwan.

Conclusions: Automated ultrasound (US)-guided PRB is a safe and reliable method of assessing childhood renal disease. A recent study shows that the presence of persistent asymptomatic isolated microhematuria in adolescents is a predictive marker of future end-stage renal disease. Hence, the emphasis of renal biopsy on children with persistent asymptomatic hematuria is beneficial for the early diagnosis of IgAN or other glomerulonephritis (GN), which tends toward progressive kidney disease in adulthood without prompt therapeutic intervention.
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At a Glance Commentary

Scientific background of the subject

Automated US-guided PRB is the safe and reliable method of either disease diagnosis or prognosis. Pathologically, MCD, LN and IgAN are possibly the most common childhood kidney disorders in Taiwan.

What this study adds to the field

In addition to renal involvement secondary to SLE, IgAN is probably the leading primary GN underlined Taiwanese children with persistently asymptomatic hematuria with/without proteinuria. Since persistent microscopic hematuria is supposed to be the risk factor associated with future renal failure, the consideration of renal biopsy among these affected children is needed to be highlighted for early diagnosis of IgAN and other severe GN.

Key words: IgA nephropathy, percutaneous renal biopsy, persistent hematuria

INTRODUCTION

Percutaneous renal biopsy (PRB) is an important diagnostic tool used to obtain renal cortical tissues for histological evaluation. As it enables diagnosis, surveillance of disease progression as well as categorizing the prognosis, RB has been recognized as the most valuable examination for assessing patients with kidney disorders. Moreover, the

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introduction of real-time ultrasound (US) guidance and the invention of automated biopsy instruments make this technique more feasible, efficient, and less risky.[1-4] Previous literature has revealed that the overall biopsy-related complication rate in pediatric patients is around 5-23%.[2,5-8] The majority developed minor bleeding complications post-PRB, including macroscopic hematuria (3-10%) and perirenal hematoma (12-42%).[1,5-8] However, some still suffered severe major bleeding complications (0.8-7%) necessitating blood transfusion or emergent surgical intervention.[1,7,9,10] On the other hand, the procedures and biopsy instruments are similar for both adults and children, but some technical modifications are needed to suit children.[6,8,11] For instance, no food intake is suggested prior to pediatric biopsies, so as to minimize the danger of choking caused by vomiting during the procedure. Additionally, the administration of a general anesthetics plus sedatives is recommended for uncooperative young children, where it is deemed to be too risky to perform renal biopsy. In our practice, a combination of ketamine and midazolam used to be prescribed for children younger than 10 years of age, whereas only local analgesia was given to children older than 10 years of age. In the present study, the aim was to investigate the safety and efficiency of pediatric PRB. Meanwhile, we also evaluated the patterns of childhood renal disease in Taiwan, based on the histological features.

METHODS

From July 2005 to July 2009, we retrospectively reviewed the medical records of 99 consecutive native PRBs performed on 91 children, consisting of 43 girls (mean age, 11.6 ± 4.3 years) and 48 boys (mean age, 10.2 ± 4.4 years), in the Pediatric Nephrology Unit of the Chang Gung Children's Hospital, Linkou Medical Center, in Taiwan. Patients who presented with abnormal urinalysis such as proteinuria ± hematuria, persistent asymptomatic isolated hematuria or unexplained renal function impairment were identified for PRBs [Table 1]. Of 91 biopsied children, five cases with lupus nephritis (LN) and one with IgA nephropathy (IgAN) received PRBs twice, and a boy who was diagnosed with post-infectious glomerulonephritis received PRBs thrice for guiding clinical treatments and determining the outcome. Comprehensive medical histories, laboratory and physical examinations, and image studies (US and intravenous pyelogram or computed tomography (CT) were implemented preceding renal biopsy. Structural abnormalities such as the nutcracker syndrome, hydronephrosis, urolithiasis, renal tumor, and hypercalciuria were excluded in all cases. All PRBs were conducted by the same pediatric nephrologist, with an automated 18-gauge needle gun, under US guidance.

Table 1: Indications for PRBs in 91 children

Indication	No. of patients (%)
SLE with renal involvement	32 (35.2)
Nephrotic syndrome	
Frequent relapsing steroid dependent	12 (13.2)
Steroid-resistant	3 (3.3)
Age-related (<1 year or >10 years)	12 (13.2)
Persistent hematuria with mild-to-heavy proteinuria*	18 (19.8)
Persistent isolated hematuria†	4 (4.4)
Unexplained renal failure	9 (9.9)
Isolated proteinuria	1 (1.0)
Total	91 (100)

*Mild to heavy proteinuria ranging between 100 and 500 mg/dl;
†Asymptomatic isolated hematuria was defined as more than 20 RBCs/uL in urine with undetectable proteinuria

Pre-renal biopsy preparation

Written informed consent was obtained from the parents or legal guardians prior to the renal biopsy. Detailed family and personal medical histories were taken, with an emphasis on histories of hereditary bleeding disorders or use of particular drugs such as aspirin, dipyridamole or warfarin, which are known to increase the risk of prolonged bleeding. Additionally, children who had significant hypertension were avoided until they had been treated adequately. Initial laboratory examinations included serum creatinine (Scr), blood urea nitrogen, electrolytes, hemoglobulin concentration, platelet count, prothrombin time, activated partial thromboplastin time, bleeding time, and urinalysis. Coagulopathy was absolutely contraindicated for PRB. Renal biopsy could be not considered until it was corrected by transfusion of fresh frozen plasma or platelets. Once prolonged bleeding time, equal to or greater 10 minutes, was found in patients with renal dysfunction, the administration of a cryoprecipitate was recommended, and repeats were necessary to ensure that the abnormal bleeding tendency was corrected.

Renal biopsy procedure

A general anesthetic (ketamine at 1-2 mg/kg) plus sedative (midazolam at 0.05-0.1 mg/kg) were routinely given intravenously to children aged 10 years or younger, undergoing PRB, whereas patients over 10 years of age were prescribed only local anesthesia (1-2% xylocaine). In some cases, eperidine was given intramuscularly to those children who feared pain. Fasting for four to six hours was recommended to reduce the risk of aspiration caused by vomiting. During the procedure, the patients were in a prone position. Both the puncture site and biopsy equipment were disinfected after locating the lower pole of the kidney by US. The same pediatric nephrologist executed RB using an automated

18-gauge needle gun under direct US guidance. At least two passes were performed in each biopsy, and the renal tissues obtained were sent for routine histological studies including light microscopy (Hematoxylin and Eosin stain and Periodic acid-Schiff stain), immunofluorescence (e.g., C3, IgA, IgG, IgM, and C1q), and electron microscopy.

Post-biopsy care

After PRB, the patients required bed rest and remained in the hospital overnight for close observation of the heart rate and blood pressure. The patients were restricted by lying down in the prone position, particularly in the first eight hours, and a 0.5 kg sandbag was placed on the puncture site to boost the compression. In addition to urinalysis, a hemoglobin concentration test and follow-up US were arranged for the next day. If patients remained hemodynamically stable and did not experience unbearable discomfort or major bleeding complications, they were safely discharged and visited the Outpatient Department within one week after discharge. We also advised limited physical activity during this period.

Statistical analysis

The statistical data were analyzed by the Student's two-tailed *t*-test, Pearson's correlation coefficients, and the non-parametric test using the SPSS version 19.0. $p < 0.05$ was considered to be significant.

RESULTS

The mean number of glomeruli obtained per biopsy was 19 ± 10, and at least two passes were practiced in each PRB. Adequate renal tissue for histological diagnosis was achieved in 99% of the cases except for one, which had insufficient glomeruli (<5). As shown in Table 2, 3.0% (3/99) of the children developed transient gross hematuria following PRBs, and 11.1% (11/99) had perirenal hematoma. Some patients complained of temporary flank pain after the eight-hour compression from using a sand bag placed on the puncture site. None of patients encountered major bleeding complications requiring medical intervention, such as blood transfusion, angiography embolization, emergent nephroectomy, or any sedation-related complications. These minor bleeding complications resolved spontaneously between the two-week and three-month follow-ups. Furthermore, the occurrence of biopsy-related bleeding complications was not related to age, gender, or the underlying kidney disease [Table 2]. In Table 1, it is shown that systemic lupus erythematosus (SLE) with renal involvement was the most frequent indication of renal biopsy (35.2%, 32/91) for both male and female pediatric patients; 13.2% (12/91) and 3.3% (3/91) of the PRBs were performed on children who presented with Frequent-Relapsing Steroid-Dependent Nephrotic Syndrome (FRSDNS) and Steroid-Resistant Nephrotic Syndrome (SRNS). Besides, 13.2% (12/91) of the nephrotic pediatric patients, whose age was less than one year or over 10 years, underwent PRBs due to a poor response to corticosteroid treatment within the initial six weeks. This was because there is a likelihood of Focal Segmental Glomerulonephritis (FSGS) or Mesangial Proliferative Glomerulonephritis (MPGN), which have poor prognosis compared to Minimal Change Disease (MCD). Children with persistent asymptomatic hematuria (≥20 RBC/uL in urine) were advised to receive kidney biopsies for disease determination, especially if mild or moderate proteinuria (100-500 mg/dL) was coexisting (24.2%, 22/91). Also, 9.9% (9/91) of the PRBs were performed in patients who had unexplained renal failure.

Table 3 shows that LN (35.1%), particularly World Health Organization (WHO) class IV (23.0%), MCD (22.0%), and IgAN (13.2%), were the major kidney diseases in pediatric patients diagnosed with SLE, nephrotic syndrome, and persistent asymptomatic hematuria with or without mild-to-moderate proteinuria.

Table 2: Comparisons of 99 biopsies performed in 91 children with and without the bleeding complication

	(+) Bleeding complications after RB *n*=14	(-) Bleeding complications after RB *n*=85	Significant*
Gender	M:F=8:6	M:F=45:40	NS
Age (years)	8.77±5.81	11.27±4.23	NS
Number of glomeruli obtained per biopsy	17.2±9.9	19.8±10.3	NS
Underlying renal disease			NS
Cystic kidney disease	1		
FSGS	1†		
IgAN	3		
LN	4		
MCD	2¥		
Congenital NS	1		
MPGN	1		
PSGN	1¥		

*NS not significant, $p>0.05$; †Three cases (1 FSGS, 1 PSGN, and 1 MCD) suffered transient gross hematuria and 11 were found with perirenal hematoma after renal biopsy. Abbreviations: FSGS: Focal segmental glomerulonephritis; IgAN: IgA nephropathy; LN: Lupus nephritis; MCD: Minimal change disease; MPGN: Mesangial proliferative glomerulonephritis; PSGN: Post-streptococcal glomerulonephritis

DISCUSSION

Serum creatinine and proteinuria are the conventional biomarkers used to diagnose kidney disease, but some limitations restrict their clinical use. Scr is not raised until renal injury is well-established, which delays the identi-

Table 3: Histopathological diagnosis of 91 biopsied pediatric patients

	Cases (%)
Primary glomerular disease	
Nephrotic syndrome	
MCD	20 (22.0)
FSGS	4 (4.4)
IgM nephropathy	1 (1.1)
Mesangial proliferation	1 (1.1)
Congenital nephrotic syndrome	1 (1.1)
IgA nephropathy	12 (13.2)
Mesangioproliferative GN	1 (1.1)
Post-streptococcal GN	5 (5.5)
Crescentic GN	2 (2.2)
Glomerulosclerosis	1 (1.1)
Minor glomerular abnormalities	1 (1.1)
Secondary glomerular disease	
Lupus nephritis	
WHO class I	1 (1.1)
WHO class II	4 (4.4)
WHO class III	3 (3.3)
WHO class IV	21 (23.0)
WHO class V	2 (2.2)
WHO class VI	1 (1.1)
Henoch-Schönlen Purpura (HSP) nephritis	2 (2.2)
ANCA vasculitis	1 (1.1)
Hereditary and congenital disease	
Alport syndrome	1 (1.1)
Thin basement membrane disease	1 (1.1)
Cystic kidney disease	1 (1.1)
Tubulointerstitial nephritis	2 (2.2)
Aristolochic acid nephropathy	1 (1.1)
Unclassified	1 (1.1)
Total	91 (100)

Abbreviations: MCD: Minimal change disease; FSGS: Focal segmental glomerulonephritis; GN: Glomerulonephritis

fication of the disease. Although the level of proteinuria has good correlation with the degree of kidney damage, it is impossible to discriminate it from acute inflammation, which will respond to steroid or immunosuppressive treatment to chronic irreversible fibrosis. Hence, thus far RB has been the standard method for assessing patients with kidney disease. In comparison to Scr and proteinuria, RB is an invasive examination. Nevertheless, the introduction of real-time US-guided PRB and automated biopsy guns significantly improve the diagnostic accuracy and reduce the risk of biopsy-related complications as well. The overall complication rate of inpatient PRBs in children was around 5.2 ~ 23.5%, whereas the complication rate of outpatient PRBs was 2.6 ~ 11.4%. The lower complication rate of outpatient PRBs might be due to underestimation. Although some suggested that pediatric outpatient RBs were practical in terms of cost savings,[9,12-14] the optimal time for bed rest and in-hospital observation after biopsy remains controversial. Previous studies reported that a minimum of six to twelve hours of observation was required to detect major bleeding complications. For renal function impairment patients, a longer 23- to 24-hour observation was advised, as they were in danger of bleeding post PRB.[15,16]

In addition to pre-biopsy fasting, we routinely prescribed general anesthesia, a combination of ketamine and sedatives, for children aged 10 years or younger, whereas, a local anesthetic was used for children greater than 10 years of age. Besides, an 18-gauge needle was adopted in all pediatric PRBs. Even though a 16-guage needle was considered to have good diagnostic yield, the higher rate of bleeding complications were a concern.[6] Compared to the use of a 16-guage needle, our result showed that an 18-gauge biopsy needle had similar efficiency and was much safer.

Since August 1990, mass urinary screening has been executed in elementary and junior high-school students in Taiwan. Many children have been taken to hospital for further evaluation if abnormal urinalysis persisted. For those who presented with heavy proteinuria, renal function deterioration, or renal involvement as part of a systemic or autoimmune disorder, RB was a clear-cut indication for disease identification. However, the consideration and optimal timing of RB in children with persistent asymptomatic isolated microscopic hematuria are inconclusive.

As the matter of fact, hematuria is not an uncommon finding of routine urinalysis in children. Murakami M *et al*. conducted a 13-year cross-sectional study to determine the prevalence of asymptomatic urine abnormalities in school children aged six to fourteen years in Japan.[17] Their data suggested that the prevalence of asymptomatic hematuria (6-20 RBC/HPF) in elementary and junior-high school students was 0.37 and 0.94%, respectively, whereas, the prevalence of proteinuria in elementary and junior-high school students was 0.08 and 0.54%, respectively. Furthermore, it was reported that 9.3% of Japanese school children presented with hematuria (≥6 RBC/mm^3 in uncentrifuged urine).[18] In Taiwan, Lin *et al*., analyzed 513 school children, who were identified with various gradings of persistent urine abnormalities [microscopic hematuria only, light proteinuria (30-100 mg/dl), combined with microscopic hematuria and light proteinuria, and heavy proteinuria (>100 mg/dl)].[19] In their study, it showed that 46.4% had persistent isolated microhematuria, and 14.3% had persistent microhematuria with associated light proteinuria. The remaining 39.3% had proteinuria. SLE with renal involvement was the major secondary GN, and severe form of LN could occur in children with persistent microscopic hematuria, but without proteinuria. Also, their result suggested that IgAN and other nephritis had an important role to play in children who had persistent isolated hematuria as well as those who had co-existing proteinuria.

Similarly, our study showed that regardless of gender, LN was the principal cause leading to childhood renal disease. With a poor link between clinical presentation, urinalysis, and the pathohistological patterns of LN, RB becomes the standard examination for the early diagnosis of severe LN. Moreover, for patients who are more than 10 years old and have severe renal disease underlined with SRNS, FRSDNS, and NS, RB is indicated. As a result, only one case of FRSDNS was diagnosed with FSGS. MCD remains the leading cause of childhood nephrotic syndrome.

In the present study, PRBs were performed on 22 children with persistent asymptomatic hematuria. As shown in Tables 4 and 5, 12 (54.5%) were confirmed with IgAN. Among these patients, four of them (No. 3, 8, 9, 12) clinically presented with persistent asymptomatic isolated hematuria, and the majority had minor glomerular abnormality at diagnosis, except one case (No. 9). Looking at the patient (No. 11), this boy received a repeat biopsy at the remission stage after one-year, combined glucocorticosteroid and cyclophosphamide treatment. Despite clinical stabilization and only microscopic hematuria seen in urinalysis, there was no remarkable histological improvement in his kidneys.

Several literatures have shown that IgAN is the common primary etiology underlying children who have persistent microscopic hematuria, with or without associated proteinuria.[17-20] Moreover, proteinuria over 0.5 g/day is suggested as a late manifestation in IgAN.[21,22] The latest nationwide, population-based retrospective cohort study was conducted to assess the long-term outcome of adolescents and young adults with persistent asymptomatic isolated microscopic hematuria, in Israel.[23] During the almost 22-year follow-up, they had found that there was a remarkably higher incidence of patients treated for end-stage renal disease (ESRD) as opposed to patients without persistent asymptomatic isolated microscopic hematuria, 34.0 and 2.05 per million people, respectively. Furthermore, primary GN, including IgAN, was attributed to more than 50% of these ESRD patients. Their fundamental finding suggested that persistent asymptomatic isolated microscopic hematuria among young people can be a marker of predicting progressive kidney disease. This emphasizes the significance of the early detection of unknown renal disease, before the nephritic symptoms and signs are seen. As clinical features and laboratory examination are not adequate enough to make the diagnosis of either IgAN or subtypes of LN, RB is believed as the most trustworthy method for identifying the disease at an early stage.

It is known that there is a higher prevalence and incidence of ESRD in Taiwan. In addition to the potential

Table 4: Demographic characteristics of 12 persistently hematuric pediatric patients who were diagnosed with IgAN

Patient no.	Gender	Age	Clinical presentations	Proteinuria at diagnosis (g/day)	IgAN subtypes *	Follow-up duration before renal biopsy
1	Female	13 years 6 months	Nephrotic syndrome, history of persistent microscopic hematuria	10.13	IgAN IV	7 days
2	Male	15 years 3 months	History of persistent microscopic hematuria, hypertension	1.24	IgAN I	15 days
3	Female	9 years 3 months	Persistent asymptomatic microscopic hematuria	0.39	IgAN I	1.7 years
4	Female	10 years 11 months	Persistent microscopic hematuria	1.34	IgAN I	7 years
5	Male	10 years	Persistent micro- and macroscopic hematuria	3.24	IgAN III	2 months
6	Male	15 years 8 months	Persistent microscopic hematuria, renal function impairment	8.08	IgAN V (ESRD)	7 years
7	Female	14 years 9 months	Persistent asymptomatic microhematuria	2.0	IgAN IV	2.5 years
8	Male	6 years	Persistent asymptomatic micro- and macroscopic hematuria	0.32	IgAN I	1.3 years
9	Male	7 years	Persistent asymptomatic micro- and macroscopic hematuria	0.13	IgA N IV	3 months
10	Male	6 years 3 months	History of persistent asymptomatic micro- and macroscopic hematuria	3.29	IgAN III	22 days
11	Male	4 years	Renal impairment, history of persistent microscopic hematuria	4.05	IgAN IV (60% crescents)	9 days
		5 years	Normal renal function, microscopic hematuria	0.05	IgAN IV †(60% crescents)	
12	Female	12 years 3 months	Persistent asymptomatic microscopic hematuria	0.26	IgAN I	6 years

*Haas system of classification for Ian,[20] †A repeat renal biopsy after a one-year combined treatment of cyclophosphamide and corticosteroid.
Abbreviation: IgAN: IgA nephropathy

Table 5: The distribution of histological diagnosis among 22 children with persistent asymptomatic hematuria with and without mild-to-moderate proteinuria

	Number of patients, *n*=22 (%)	
	Persistent isolated hematuria (*n*=4)	Persistent hematuria± mild-to-moderate proteinuria (*n*=18)
IgA nephropathy	4 (18.18)	8 (36.36)
Tubulointerstitial nephritis		2 (9.09)
HSP nephritis		2 (9.09)
Thin basement membrane disease		1 (4.55)
Mesangioproliferative GN		1 (4.55)
Alport syndrome		1 (4.55)
Cystic kidney disease		1 (4.55)
Minor glomerular abnormalities or unclassified		2 (9.09)

risk factors (e.g., hypertension, diabetes, and use of illegal Chinese herbs), the attribution of primary GN, such as, IgAN to ESRD, to patients with unknown etiologies is unclear, and it is probably underestimated due to the delay of diagnosis. Without prompt therapeutic intervention, uninterrupted subtle inflammation can begin in IgAN children, which will result in irreversible renal fibrosis in adulthood. Therefore, even though there is no need for intensive medication at the early stage of the disease, children and their parents can benefit from more medical advice and support throughout the subsequently longstanding follow-up.

However, there are some limitations to this study. The number of children with persistently asymptomatic hematuria is small and a longer observation is also required to ascertain the benefit of ameliorating long-term renal survival.

Conclusion

Real time US-guided PRB with a biopsy gun is a safe and effective examination in children with kidney disease. Our result showed that LN, MCD, and IgAN were the most common childhood kidney diseases in Taiwan. In the study, it also highlighted that IgAN is an important cause of primary glomerular disease in children who present with persistent asymptomatic hematuria, with and without associated proteinuria. As persistent asymptomatic microscopic hematuria was suggested as a poor renal prognostic indicator, RB should be emphasized for early detection of asymptomatic patients, who are at risk of progressive renal disease.

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