The pathological spectrum of pediatric kidney disease: 18-Year experience from a single tertiary care center in northern Taiwan

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IgA nephropathy; Lupus nephritis; Minimal change disease

Abstract  Background: Glomerular disease is one of the leading causes of chronic kidney disease in children worldwide. Recent studies outlined the changing spectrum of glomerular disease in certain countries. Therefore, our study aimed to evaluate the histopathological patterns and changes in pediatric kidney disease over the past 18 years in northern Taiwan.

Methods: This was a retrospective chart review study of pediatric patients (<18 years of age) undergoing percutaneous renal biopsies (PRBs) of native kidneys between January 2002 and July 2020 from a Pediatric Care Center at Chang Gung Memorial Hospital, Taoyuan, Taiwan.

Results: This study analyzed a total of 339 pediatric native PRBs. The mean age of the subjects was 13.7 ± 7.0 years (184 girls and 155 boys). The most common indications of PRBs included acute nephritic syndrome (55.7%), idiopathic nephrotic syndrome (22.7%), persistent asymptomatic hematuria (13.9%), and unexplained renal failure (7.7%). Our study revealed that proliferative lupus nephritis (LN), minimal change disease (MCD)-related nephrotic syndrome, and IgA nephropathy (IgAN) were the most frequent biopsy-proven pediatric glomerular diseases. In addition, we showed that severe acute post-streptococcal glomerulonephritis (APSGN) was infrequent and has not even been diagnosed since 2010.

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1. Introduction

Glomerular disease remains a major cause of pediatric chronic kidney disease (CKD) across the globe and predominates in developing countries and regions, such as India, Southeast Asia, Latin America, the Caribbean, and Sub-Saharan Africa.\(^1\)\(^-\)\(^3\) Overwhelmingly, all forms of glomerulonephritis (GN) share the tendency of rapid progression to end-stage renal failure, compared with CKD in children affected by congenital anomalies of the kidney and urinary tract. Numerous studies have already disclosed that the diagnosis and outcome of glomerular disease differ significantly between age groups (adults and children), sexes, and races.\(^4\)\(^-\)\(^5\) Furthermore, accumulating evidence indicates its multifactorial and heterogenous pathogenic mechanism, displaying the crucial roles of genetics and gene–environment interactions in the development and progression of kidney disease.\(^6\)\(^-\)\(^7\) Particularly, exposure to environmental risk factors, such as air pollution, heavy metals, and other environmental pollutants (e.g., aristolochic acids, pesticides, phthalates, and bisphenol A), as well as infections, is responsible for altering the frequency of glomerular disease.\(^8\)

Recently, Nie et al. conducted a nationwide survey consisting of 7962 pediatric kidney biopsies from 115 hospitals across China from January 2004 to December 2014.\(^5\) They found that the proportion of biopsies positive for membrane nephropathy (MN) increased from 3% to 7% in the past 10 years. Another study by Xu et al. also reported a similar increasing trend in MN among the adult population in China. They assumed that the changing spectrum of glomerular disease was most likely associated with long-term exposure to air pollution.\(^9\) Meanwhile, an altered profile of kidney disease was also observed in other countries.\(^10\)\(^-\)\(^11\) In Taiwan, over the past decades, growing public awareness of the control and prevention of infectious disease and environmental hazards has led to public health promotion. For instance, leaded gasoline was banned in 2000 to reduce environmental exposure to lead.\(^12\) Soon after, aristolochic-acid-containing Chinese herbal products were also prohibited due to their nephrotoxicity and carcinogenicity.\(^13\) Furthermore, increased immunization coverage by the Taiwan National Health Insurance Program since 1995 has been highly effective at reducing the burden of vaccine-preventable infectious diseases.

In this 18-year, retrospective study, we aimed to estimate the epidemiological profiles and overall changes in biopsy-proven pediatric kidney disease over time from a pediatric tertiary care center after the implementation of these polices in Taiwan.

2. Methods

2.1. Participants and study design

This retrospective chart review study was conducted at Lin-Kou Chang Gung Memorial Hospital in Taoyuan, Taiwan during the period from January 2002 to July 2020. A total of 339 pediatric patients aged between 0 and 18 years (184 girls and 155 boys) undergoing ultrasound-guided percutaneous renal biopsies (PRBs) of native kidneys were enrolled in the study. Frequent indications of PRBs included isolated moderate-to-severe proteinuria, defined as 24-h urine protein >1 g/day or a morning spot urine protein-to-creatinine ratio (UPCR) >1 g/g; idiopathic nephrotic syndrome (INS), characterized by nephrotic range proteinuria >40 mg/m\(^2\)/hour or UPCR >2 g/g, hypoalbuminemia, hyperlipidemia, and edema; persistent asymptomatic hematuria with/without proteinuria; unexplained renal impairment; and acute nephritis syndrome secondary to autoimmune disorders such as systemic lupus erythematosus (SLE) or others. To investigate the epidemiological profiles and overall changes in pediatric kidney biopsies over the past 18 years, we divided the participants into two groups depending on the date on which the biopsy procedure was performed in two different consecutive periods, between January 2002 and December 2010 (2002–2010) and between January 2011 and July 2020 (2011–2020). In addition, our study assessed gender and age differences in kidney disease frequencies during the study period. The study was approved by the Ethics Committee of Lin-Kou Chang Gung Memorial Hospital, Taoyuan, Taiwan (IRB approval number: 201900820A3, December 15, 2019). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

3. Results

3.1. Practice and demographic characteristics of pediatric patients undergoing PRBs

As shown in Table 1, the most frequent indication for PRBs was acute nephritis secondary to certain autoimmune disorders (55.7%), especially SLE (41.0%). The second most common indication was INS (22.7%), including 11.8% of INS children aged ≥12 years, 9.7% of steroid-sensitive NS (SSNS), and only 1.2% of steroid-resistant NS (SRNS). Among
Table 1  The common indications of PRBs in our 339 pediatric patients.

| Indications                               | Total, n (%) |
|-------------------------------------------|--------------|
| Acute nephritis syndrome                   | 189 (55.7)   |
| SLE with renal involvement                | 139 (41.0)   |
| Related to other disease or medications   | 50 (14.7)    |
| Idiopathic nephrotic syndrome             | 77 (22.7)    |
| Steroid-sensitive NS                      | 33 (9.7)     |
| Delay response to steroid or decreased     | 11 (3.2)     |
| renal function under CNI                   |              |
| Frequent relapsing NS                     | 14 (4.1)     |
| Steroid-dependent NS                      | 8 (2.4)      |
| Children aged ≥12 years                   | 40 (11.8)    |
| Steroid-resistant NS                      | 4 (1.2)      |
| Persistent asymptomatic hematuria          | 47 (13.9)    |
| Concomitant proteinuria                   | 37 (10.9)    |
| Isolated microscopic hematuria            | 10 (3.0)     |
| Unexplained renal impairment              | 26 (7.7)     |
| **Total**                                 | **339 (100)**|

Abbreviations: SLE, systemic lupus erythematosus; NS, nephrotic syndrome; CNI, calcineurin inhibitors.

SSNS cases, PRBs were commonly executed in the affected children, presenting frequent relapsing NS (FRNS) (4.1%), delayed response to steroids, or decreased renal function under calcineurin inhibitors (CNI) such as cyclosporine or tacrolimus (3.2%), and steroid-dependent NS (SDNS) (2.4%). Other common indications consisted of persistent asymptomatic hematuria with mild proteinuria (10.9%), persistent isolated microscopic hematuria (3.0%), and unexplained renal impairment (7.7%).

Table 2 illustrates gender differences in the clinical and histopathological manifestations of 339 children and adolescents undergoing PRBs over the period from 2002 to 2020 in our hospital. The mean age at the time of renal biopsy for histological diagnoses was 13.6 ± 7.0 years (184 girls aged 15.5 ± 7.1 years and 155 boys aged 11.4 ± 6.1 years, P < 0.001). Female pediatric patients with kidney disease requiring PRBs were older than male ones, regardless of the time period, from 2002 to 2010 (girls aged 12.9 ± 6.1 years vs. boys aged 10.6 ± 4.7 years, P = 0.034) and from 2011 to 2020 (girls aged 16.6 ± 7.2 years vs. boys aged 11.8 ± 6.7 years, P < 0.001). This could be the result of a significantly higher prevalence of lupus nephritis (LN) in female pediatric patients (31.3% vs. 9.7%, P < 0.001). According to the International Society of Nephrology and the Renal Pathology Society (ISN/RPS) classification, the most frequent histological subtype was class IV (diffuse proliferative) LN (16.2% vs. 6.8%, P < 0.001), followed by class III (focal proliferative) LN (4.7% vs. 0.6%, P = 0.002) and class V (membranous) LN (2.4% vs. 0.3%, P = 0.035). The female-to-male ratio was approximately 3:1 in our pediatric lupus patients with LN. On the other hand, a relative predominance of male pediatric patients was observed in other forms of acute nephritis secondary to non-lupus autoimmune kidney disease or medications (8.8% vs. 5.9%, P = 0.014) (Supplementary Table 1).

In our cohort, boys had a higher rate of INS than girls (14.4% vs. 8.3%, P < 0.001), and the vast majority of cases were SSNS and MCD (P < 0.001). MCD was also the common pathological type of adolescent-onset INS (children ≥12 years), but there was no statistically significant gender difference. Moreover, male predominance was significant in children with persistent hematuria with and without mild proteinuria (8.3% vs. 5.6%, P = 0.04), and half of the affected boys (20/47) were diagnosed with primary IgAN.

### 3.2. Age distribution, histopathological profiling, and changes in pediatric kidney disease

Table 3 shows the comparisons of histopathological profiles and changes across the two different consecutive periods, from 2002 to 2010 and from 2011 to 2020, and the age disparity in disease patterns among the two groups, children aged <12 years and adolescents aged 12–18 years. Our results uncovered that pediatric LN, MCD, and IgAN were the most common histopathological diagnoses of pediatric kidney disease over the past two decades. Clearly, LN was more prevalent in female lupus pediatric patients and the older age group of adolescents (12–18 years old). We also found a rising tendency of pediatric LN, especially class IV LN, over time across the study period. However, this change was not statistically significant (Supplementary Fig. 1). The age disparity and the changing pathological spectrum of pediatric kidney disease, including MCD, IgAN, focal segmental glomerulosclerosis (FSGS), tubulointerstitial disease (TID), Henoch-Schönlein purpura nephritis (HSPN), thrombotic microangiopathy (TMA), anti-neutrophil cytoplasmic antibody (ANCA)-associated GN, and hereditary disease, were also insignificant. Moreover, our study showed that severe APSGN was rare and infrequent, particularly in adolescent patients, and this bacterial-infection-related GN had not even been diagnosed since 2010.

### 4. Discussion

In this 18-year, retrospective study conducted at our hospital in northern Taiwan, LN, MCD-related INS, and primary IgAN remained the leading causes of biopsy-proven kidney disease in children and adolescents. Moreover, we found no significant changes in the histological patterns of pediatric kidney disease during the study period from 2002 to 2020.

Our cohort revealed that more than one third of biopsied cases were lupus patients, especially older children and adolescents, and proliferative LN was the most common biopsy-proven pediatric kidney disease. Numerous studies have already reported that Asian SLE patients had a higher frequency of nephritis than Caucasian SLE patients (50%–60% vs. 30%–38%). Moreover, childhood-onset SLE exhibits a more aggressive disease course and higher disease activity than adult-onset SLE, leading to morbidity, mortality, and irreversible damage to major organs, especially the kidneys, brain, and blood systems. In a 20-year, retrospective Taiwanese study of childhood-onset SLE cases, approximately 60% of pediatric lupus patients had LN at the time of initial presentation, and class IV LN was the most prevalent histological subtype in more than half of pediatric lupus patients at onset. The same disease spectrum of...
pediatric lupus was also found in Southeast Asian countries; proliferative LN was the most common histological diagnosis, and more severe disease occurred there than in western cohorts. Therefore, it is apparent that SLE-related GN is an important etiology of pediatric CKD in Asia.

MCD was the most prevalent pathology of INS among Taiwanese children and adolescents and more frequent in young boys than in girls, in close agreement with findings in other countries. In this study, PRBs were performed in 77 pediatric patients with INS, and nearly half of them (40/77) were older than 12 years because numerous studies have suggested that adolescent-onset INS has clinical and histopathological features distinct from those of early childhood INS. Our results eventually revealed, over the past two decades that MCD accounted for most teenage INS patients, and only 14 pediatric patients aged 12–18 years were diagnosed with non-MCD pathologies (13 cases of FSGS and one case of IgM nephropathy). Moreover, the estimated incidence of childhood INS was approximately 3.4/100,000 children per year, and the male-to-female ratio was 1.83, based on patient data taken from our hospital over the past two decades.

Our result showed that primary IgAN was the third most common biopsy-proven kidney disease in children and adolescents who had persistent asymptomatic hematuria. In close agreement with previous studies, there was a relative predominance of males. IgAN is known as the commonest primary GN worldwide, especially in Asian countries such as Japan, China, South Korea, and Taiwan. In Taiwan, widespread urinary screening has been implemented in school-aged children since 1990. This policy may facilitate early diagnosis and prompt intervention in children with kidney disease. Thus, among our pediatric cases diagnosed with IgAN, almost all of them had excellent outcomes, and only one case who had renal function impairment at the time of diagnosis developed CKD.

Recently, an increasing prevalence of idiopathic MN in pediatric and adult patients was reported in certain countries, such as China and Singapore, which is suspected to be related to fine particulate air pollution. On the other

| Table 2 Gender differences in clinical and histopathological manifestations of 339 biopsied pediatric patients. |
| Characteristics | Total, n = 339 (100%) | Boys, n = 155 (45.7%) | Girls, n = 184 (54.3%) | P-value |
|-----------------|----------------------|----------------------|----------------------|---------|
| Age at the time of renal biopsy (years) | 13.6 ± 7.0 | 11.4 ± 6.1 | 15.5 ± 7.1 | <0.001* |
| Between 2002 and 2010 | 11.8 ± 5.6 | 10.6 ± 4.7 | 12.9 ± 6.1 | 0.034* |
| Between 2011 and 2020 | 14.5 ± 7.4 | 11.8 ± 6.7 | 16.6 ± 7.2 | <0.001* |
| Clinical manifestations, n (%) | | | | |
| Nephritis syndrome | 189 (55.7) | 63 (18.5) | 126 (37.2) | <0.001* |
| Lupus nephritis | 139 (41.0) | 33 (9.7) | 106 (31.3) | <0.001* |
| ISN/RPS Class I | 5 (1.5) | 1 (0.3) | 4 (1.2) | 0.246 |
| ISN/RPS Class II | 12 (3.6) | 3 (0.9) | 9 (2.7) | 0.143 |
| ISN/RPS Class III | 18 (5.3) | 2 (0.6) | 16 (4.7) | 0.002* |
| ISN/RPS Class IV | 78 (23) | 23 (6.8) | 55 (16.2) | <0.001* |
| ISN/RPS Class V | 9 (2.7) | 1 (0.3) | 8 (2.4) | 0.035* |
| ISN/RPS Class VI | 4 (1.2) | 1 (0.3) | 3 (0.9) | 0.404 |
| ISN/RPS Class III + V | 6 (1.8) | 1 (0.3) | 5 (1.5) | 0.150 |
| ISN/RPS Class IV + V | 7 (2.1) | 1 (0.3) | 6 (1.8) | 0.092 |
| Related to other diseases or medications | 50 (14.7) | 30 (8.8) | 20 (5.9) | 0.014* |
| Idiopathic nephrotic syndrome | 77 (22.7) | 49 (14.4) | 28 (8.3) | <0.001* |
| SSNS | 33 (9.7) | 24 (7.1) | 9 (2.6) | <0.001* |
| MCD | 23 (6.8) | 18 (5.3) | 5 (1.5) | 0.001* |
| FSGS | 6 (1.8) | 4 (1.2) | 2 (0.6) | 0.300 |
| Others | 4 (1.2) | 2 (0.6) | 2 (0.6) | 0.863 |
| Age ≥12 years | 40 (11.8) | 22 (6.5) | 18 (5.3) | 0.211 |
| MCD | 26 (7.6) | 16 (4.7) | 10 (2.9) | 0.093 |
| Others | 14 (4.1) | 6 (1.8) | 8 (2.4) | 0.827 |
| SRNS | 4 (1.2) | 3 (0.9) | 1 (0.3) | 0.238 |
| MCD | 2 (0.6) | 1 (0.3) | 1 (0.3) | 0.903 |
| FSGS | 2 (0.6) | 2 (0.6) | 0 (0) | 0.123 |
| Persistent asymptomatic hematuria ± proteinuria | 47 (13.9) | 28 (8.3) | 19 (5.6) | 0.040* |
| IgAN | 34 (10) | 20 (5.9) | 14 (4.1) | 0.053 |
| Others | 13 (3.9) | 8 (2.4) | 5 (1.5) | 0.244 |
| Unexplained renal impairment | 26 (7.7) | 15 (4.4) | 11 (3.3) | 0.203 |

The comparisons between categorical variables and continuous variables are compared using the Chi-square tests and t-tests, respectively. *P value < 0.05 is considered to be statistically significant.

a Others include thin basement membrane disease, Alport syndrome, C3 glomerulopathy and insufficiency for diagnosis.
hand, our study showed the frequency of biopsy-proven pediatric kidney disease to be unchanged in northern Taiwan, and the major diseases were LN and MCD-related INS. Looking back over the past two decades on environmental and air pollution issues in Taiwan, leaded gasoline has been banned since 2000 to reduce airborne lead exposure. It is well-known that chronic lead poisoning can impair intellectual development and renal function. In addition, multiple measures, such as strict exhaust emission standards, the Taiwan air quality monitoring network, and the expansion of green spaces, also benefit air quality maintenance and improvement in this country. Furthermore, after an antibiotic restriction policy for acute respiratory tract infection and the initiation of a comprehensive immunization program in Taiwan, there was a significant decline in infections with Streptococcus pyogenes from 53.1% (1988–2000) to 10.7% (2006–2010), as well as in vaccine-preventable diseases. For instance, since the introduction of the 13-prong pneumococcal conjugate vaccine into the national childhood immunization program in March 2013, the incidence of invasive pneumococcal disease including hemolytic uremic syndrome has declined dramatically.

Thus far, there are limited studies on the epidemiology of early kidney disease in the pediatric population in Taiwan. This research can provide information relevant to the frequent indications of PRBs and kidney disease patterns among Taiwanese children and adolescents. However, there are some limitations to this study. First, our research only assessed cases from a single medical center. Clarification of the changing spectrum of pediatric renal biopsies would require more sample cases from different hospitals and medical centers across the nation. Second, biopsy policies among different regions may affect the willingness of physicians to perform this invasive procedure in clinical settings. Although the clinical indications for renal biopsies in the pediatric population are generally based on the KIDGO guidelines in our hospital, sample selection bias is a problem. In addition, we reported a significant reduction in severe APSGN cases over the past decade. However, the incidence of the mild form of APSGN is still uncertain among the pediatric population in Taiwan.

5. Conclusions

Changes in the frequency of kidney disease can be influenced by genomic and environmental factors. Effective public and environmental health interventions are beneficial for the prevention and control of environmental risk factors and related illnesses, including kidney disease. In this context, we speculated that these might contribute in part to the unchanged pathological spectrum of kidney disease in Taiwanese children and adolescents, as well as the reduced burden of infection-associated glomerular disease such as APSGN and pneumococcal-induced hemolytic uremic syndrome.

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Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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### Table 3

| Renal pathology (n) | <12 years old, n (%) | 12 – 18 years old, n (%) | P value | P value |
|--------------------|----------------------|--------------------------|---------|---------|
|                    | 2002 to 2010         | 2011 to 2020             |         |         |
| LN (139)           | 12 (21.4)            | 12 (15.4)                | 0.372   | 27 (55.1) | 88 (56.4) | 0.873 |
| MCD (61)           | 16 (28.6)            | 18 (23.1)                | 0.474   | 11 (22.4) | 16 (10.3) | 0.181 |
| IgAN (34)          | 7 (12.5)             | 7 (9.0)                  | 0.514   | 6 (12.2)  | 14 (9.0)  | 0.503 |
| FSGS (27)          | 4 (7.1)              | 10 (12.8)                | 0.293   | 3 (6.1)   | 10 (6.4)  | 0.943 |
| HSPN (7)           | 2 (3.6)              | 1 (1.3)                  | 0.381   | 0 (0)     | 4 (2.6)   | 0.260 |
| APSGN (5)          | 5 (8.9)              | 0 (0)                    | 0.007*  | 0 (0)     | 0 (0)     |       |
| ANCA-associated GN (4) | 2 (3.6)   | 2 (2.6)                  | 0.738   | 0 (0)     | 0 (0)     |       |
| TMA (4)            | 0 (0)                | 2 (2.6)                  | 0.230   | 0 (0)     | 2 (1.3)   | 0.428 |
| TID (28)           | 2 (3.6)              | 13 (16.7)                | 0.082   | 1 (2.0)   | 12 (7.7)  | 0.158 |
| Hereditary diseases (8)* | 3 (5.4) | 2 (2.6)                  | 0.404   | 0 (0)     | 3 (1.9)   | 0.331 |
| Other diseases (5)* | 0 (0)               | 2 (2.6)                  | 0.230   | 1 (2.0)   | 2 (1.3)   | 0.701 |
| Insufficiency for diagnosis (17) | 3 (5.4) | 9 (11.5)                | 0.219   | 0 (0)     | 5 (3.2)   | 0.206 |
| Total (339)        | 56 (100)             | 78 (100)                 | 49 (100) | 156 (100) |

*P value < 0.05.

* a Hereditary disease includes thin basement membrane disease, Alport syndrome, autosomal recessive polycystic kidney disease and papillonephritis (renal coloboma syndrome).

* b Others include C3 Glomerulopathy, cyanotic nephropathy, diabetic nephropathy, and IgM nephropathy.
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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2022.07.005.