

Clinicopathological features of pediatric renal biopsies in the plateau regions of China

Journal of International Medical Research
2018, Vol. 46(11) 4539–4546
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DOI: 10.1177/0300060518786908
journals.sagepub.com/home/imr



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Abstract

Objective: This study aimed to analyze the clinicopathological features of pediatric renal biopsies from plateau regions of China.

Methods: Clinicopathological features of pediatric renal biopsies were compared between plateau and non-plateau regions in patients who were admitted to West China Second University Hospital, Sichuan University between April 2001 and March 2017. Patients were children younger than 18 years.

Results: The proportion of primary glomerular disease in the plateau group was lower than that in the non-plateau group (45.56% vs 62.09%, respectively). In the plateau group, IgA nephropathy (IgAN) was the major primary glomerulonephritis (GN) pathology. IgAN accounted for 36.54% and 21.63% of GN cases with nephrotic syndrome and hematuria, respectively. Henoch-Schönlein purpura nephritis was the most common secondary GN in both groups. The proportion of hepatitis B virus-associated GN was higher and that of lupus nephritis was lower in the plateau group than in the non-plateau group.

Conclusions: There are differences in renal pathological types between children in plateau regions and those in non-plateau regions. Among children in plateau regions, IgAN and Henoch-Schönlein purpura nephritis were the most common kidney diseases.

Keywords

Renal biopsy, pathology, plateau, glomerulonephritis, nephrotic syndrome, hematuria

Date received: 1 April 2018; accepted: 6 June 2018

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Introduction

Renal biopsy is a well-established diagnostic modality for kidney diseases in children and adolescents. Renal biopsy provides nephrologists with important information for confirming a clinical diagnosis, evaluating the course and severity of the disease, and monitoring its progression and response to therapy.¹ Currently, a considerable amount of epidemiological data for pediatric renal disease patterns are available from studies of renal biopsies in different countries.²⁻⁵ However, the etiology of renal pathology varies with age, race, geographical environment, and renal biopsy indication.

There are several major inhabited plateau regions, which are mainly located in Africa (Ethiopian summits), Asia (Tibetan plateau and along the Himalayan mountains), and America (Andean mountains). The common features of the climate in plateau regions include air with low humidity and low oxygen content, strong ultraviolet radiation, and low temperatures. The diminished oxygen availability in these regions is due to a low barometric pressure. Living at a high altitude under chronic hypoxic conditions has many effects on the kidney,⁶ including reduced renal plasma flow with a preserved glomerular filtration rate, body fluid retention, blood pressure elevation, and excessive erythrocytosis.⁷ Chronic, systemic exposure to hypoxia can lead to microalbuminuria and glomerulomegaly, and may eventually develop into glomerulosclerosis and renal insufficiency. Epidemiological studies have shown a higher prevalence of end-stage renal disease and exacerbated diabetic nephropathy in individuals living at high altitude.^{4,8-10} Recently, Zhou et al.¹¹ reported that there were significant differences in the pathological types of adult kidney disease between residents of Tibetan plateau regions and the mainland plains in China. However, there

are no published data on the pattern of pediatric renal diseases in plateau regions.

Therefore, this study aimed to compare and summarize the pediatric renal clinicopathological characteristics between residents of plateau regions and plains over the past 16 years in China. We aimed to help clarify the pathological characteristics of kidney diseases in children living in plateau regions.

Methods

Patients

We analyzed renal biopsy samples that were collected in our center between April 2001 and March 2017 from children younger than 18 years old from the Division of Nephrology, Department of Pediatrics, West China Second University Hospital, Sichuan University. All of the biopsies were performed by pediatric nephrologists under ultrasound guidance using 18-gauge renal biopsy needles. Patients were excluded if five or fewer glomeruli were observed by optical microscopy or if the pathological and clinical data were incomplete. A total of 829 renal biopsies were performed. A total of 744 cases were included in the analysis because of our exclusion criteria. Our study was retrospective and thus did not require ethical approval and consent from patients.

Indications for renal biopsy

Renal biopsies were indicated according to the following criteria: (1) steroid-resistant nephrotic syndrome (NS); (2) steroid-dependent NS/frequently relapsing NS; (3) NS with hematuria, low serum complement, renal impairment, or persistent hypertension; (4) NS at an age younger than 1 year or older than 10 years; (5) NS suspected to be due to secondary causes; (6) persistent microscopic hematuria or

recurrent gross hematuria for longer than 6 months; (7) hematuria with proteinuria; (8) secondary glomerular disease; and (9) acute or chronic renal failure of unknown etiology. Steroid-resistant NS, steroid-dependent NS, and frequently relapsing NS were defined according to the standards established by the subspecialty nephrology groups of the Society of Pediatrics, Chinese Medical Association in November 2000.

Data collection

All data were obtained from the medical record database established by West China Second University Hospital, Sichuan University. The data used for analysis included sex, age, pathological diagnosis, and clinical manifestations. Pathological types were classified according to the World Health Organization recommendations. Each patient's residential address was verified by telephone. A plateau region was defined as a region with an altitude exceeding 3000 m above sea level. Patients were divided into the plateau group and non-plateau group according to the altitude of the child's residence.

Statistical analysis

Data were analyzed using SPSS 21.0 software (IBM Corp., Armonk, NY, USA). Variables were compared using the

chi-square test. A p value less than 0.05 was considered statistically significant.

Results

Demographic data

Of the 744 patients, 169 were from plateau regions and 575 were from non-plateau regions. The plateau group included 56 patients of Han nationality, 67 of Tibetan nationality, 40 of Yi nationality, and six of other ethnic groups. The non-plateau group included 561 patients of Han nationality, one of Tibetan nationality, five of Yi nationality, and eight of other ethnic groups. There was a significant difference between the ethnic distributions of the two groups ($P < 0.05$). Of the 169 pediatric patients in the plateau group, 93 were boys and 76 were girls (male to female ratio: 1.22:1). A total of 13.02% of the patients in the plateau group were 0 to 5 years old, 85.21% were 6 to 14 years old, and 1.78% were 15 to 18 years old. There were no significant differences in terms of age and sex distribution between the two groups (Tables 1 and 2).

Pathology by renal biopsy

The major diagnoses in the plateau group were secondary glomerulonephritis (GN, 53.25%), followed by primary GN (45.56%),

Table 1. Main pathological diagnoses of renal biopsy samples from children according to sex in the plateau and non-plateau groups.

Pathological diagnosis	Plateau group (n = 169)		Non-plateau group (n = 575)	
	Boys	Girls	Boys	Girls
Primary glomerular disease	43 (46.24)	34 (44.74)	236 (66.11)	121 (55.50)
Secondary glomerular disease	49 (52.69)	41 (53.95)	114 (31.93)	93 (42.66)
Hereditary glomerular disease	0	1 (1.32)	5 (1.40)	2 (0.92)
Renal tubulointerstitial disease	1 (1.08)	0	2 (0.56)	2 (0.92)
Total	93	76	357	218

Values are the number of cases (%).

Table 2. Main pathological diagnoses of renal biopsy samples from children of different ages in the plateau and non-plateau groups.

Pathological diagnosis	Plateau group (n = 169)			Non-plateau group (n = 575)		
	Age <5 years	Age 6–14 years	Age 15–18 years	Age <5 years	Age 6–14 years	Age 15–18 years
Primary glomerular disease	15 (68.18)	60 (41.67)	2 (66.67)	60 (76.92)	279 (59.49)	18 (64.29)
Secondary glomerular disease	6 (27.27)	83 (57.64)	1 (33.33)	14 (17.95)	183 (39.02)	10 (35.71)
Hereditary glomerular disease	0	1 (0.69)	0	2 (2.56)	5 (1.07)	0
Renal tubulointerstitial disease	1 (4.55)	0	0	2 (2.56)	2 (0.43)	0
Total	22	144	3	78	469	28

Values are the number of cases (%).

hereditary GN (0.59%), and tubulointerstitial disease (0.59%). There were significant differences in the proportions of major diagnoses between the two groups ($P < 0.05$). Secondary GN was the predominant histological finding in the plateau group, while primary GN (62.09%) was the most common in the non-plateau group. A small number of patients had hereditary glomerular disease and tubulointerstitial diseases in both groups.

The most common histological pattern of primary GN in the plateau group was IgA nephropathy (IgAN), followed by minor glomerular abnormalities (MGA), endocapillary proliferative GN (EnPGN), membranous nephropathy (MN), crescentic GN (CreGN), focal segmental glomerulosclerosis and sclerosing nephritis (FSGS), mesangial proliferative GN without IgA deposition (MsPGN), membranoproliferative GN (MPGN), and sclerosing GN (SGN). The most common pathology in the non-plateau group was MGA, followed by IgAN and FSGS. The proportion of IgAN in the plateau group was higher than that in the non-plateau group ($P < 0.05$) (Table 3).

The most common pathology of secondary GN in the plateau group was Henoch-Schönlein purpura nephritis, followed by hepatitis B virus-associated GN (HBV-GN) and lupus nephritis (LN) (Table 4). Henoch-Schönlein purpura nephritis was the most common secondary GN pathology in both groups. In the plateau group, the proportion of HBV-GN was higher and the proportion of LN was lower than those in the non-plateau group.

Clinicopathological features of the renal biopsy samples

As shown in Table 3, the major clinical presentations included NS and hematuria in both groups. Among cases of NS in the plateau group, IgAN was the most common lesion (36.54%), followed by MGA, MN, and FSGS. MGA was the most common pathology in the non-plateau group (44.23%), followed by IgAN and FSGS. Among cases of hematuria in the plateau group, IgAN and MGA were the most common pathologies, accounting for 61.9% and 28.57%, respectively. Similarly, IgAN and MGA were the most common

Table 3. Clinicopathological features of primary glomerular disease in the plateau and non-plateau groups.

Pathological diagnosis	NS		Hematuria pending diagnosis		AGN		RPGN		CGN		Proteinuria		Total	
	Plateau	Non-plateau	Plateau	Non-plateau	Plateau	Non-plateau	Plateau	Non-plateau	Plateau	Non-plateau	Plateau	Non-plateau	Plateau	Non-plateau
MGA	17 (32.69)	92 (44.23)	6 (28.57)	55 (44)	0	3 (25.00)	0	0	0	0	0	2 (100)	23 (29.87)	152 (42.58)
IgAN	19 (36.54)	45 (21.63)	13 (61.9)	53 (42.4)	0	1 (8.33)	0	1 (100)	0	0	0	0	32 (41.56)	100 (28.01)
MsPGN	2 (3.85)	18 (8.65)	1 (4.76)	13 (10.40)	0	1	0	0	0	0	0	0	3 (3.90)	32 (8.96)
MPGN	0	0	0	0	0	0	0	0	1 (100)	0	0	0	1 (1.30)	0
MIN	4 (7.69)	9 (4.33)	0	1 (0.80)	0	0	0	0	0	0	0	0	4 (5.19)	10 (2.80)
EnPGN	2 (3.85)	9 (4.33)	1 (4.76)	0	2 (100)	7 (58.33)	0	0	0	0	0	0	5 (6.49)	16 (4.48)
CreGN	3 (5.77)	1 (0.48)	0	0	0	0	1 (100)	0	0	0	0	0	4 (5.19)	1 (0.28)
FSGS	4 (7.69)	30 (14.42)	0	3 (2.4)	0	0	0	0	0	0	0	0	4 (5.19)	33 (9.24)
SGN	1 (1.92)	4 (1.92)	0	0	0	0	0	0	0	9 (100)	0	0	1 (1.30)	13 (3.64)
Total	52	208	21	125	2	12	1	1	1	9	0	2	77	357

Values are the number of cases (%). NS, nephrotic syndrome; AGN, acute glomerulonephritis; RPGN, rapid progressive glomerulonephritis; CGN, chronic glomerulonephritis; MGA, minor glomerular abnormalities; IgAN, IgA nephropathy; MsPGN, mesangial proliferative glomerulonephritis without IgA deposition; MPGN, membranoproliferative glomerulonephritis; MIN, membranous nephropathy; EnPGN, endocapillary proliferative glomerulonephritis; CreGN, crescentic glomerulonephritis; FSGS, focal segmental glomerulosclerosis and sclerosing nephritis; SGN, sclerosing glomerulonephritis.

Table 4. Main diagnoses of non-primary glomerulonephritis in the plateau and non-plateau groups.

Diagnosis	Plateau group (n = 92)	Non-plateau group (n = 218)	Total (n = 310)
Secondary glomerular disease	90 (100)	207 (100)	297 (100)
Henoch-Schönlein purpura nephritis	71 (78.89)	135 (65.22)	206 (69.36)
Lupus nephritis	6 (6.67)	45 (21.74)	51 (17.17)
HBV-associated glomerulonephritis	11 (12.22)	11 (5.31)	22 (7.41)
ANCA-associated glomerulonephritis	1 (1.11)	4 (1.93)	5 (1.68)
Hemolytic uremic syndrome	0 (0)	3 (1.45)	3 (1.01)
Others	1 (1.11)	9 (4.35)	10 (3.37)
Hereditary glomerular disease	1 (100)	7 (100)	8 (100)
Hereditary nephritis	1 (100)	4 (57.14)	5 (62.50)
Thin basement membrane nephropathy	0	3 (42.86)	3 (37.50)
Renal tubulointerstitial disease	1 (100)	4 (100)	5 (100)

Values are the number of cases (%). HBV, hepatitis B virus; ANCA, anti-neutrophil cytoplasmic antibody.

pathologies in the non-plateau group, accounting for 44% and 42.4%, respectively.

Discussion

Our study examined data regarding the pathological characteristics of renal biopsy samples from a pediatric population in plateau regions over 16 years. Our hospital is a tertiary referral hospital in Southwest China, and we treat many children from the Qinghai Tibet Plateau. There have been no previous studies of kidney biopsy samples from the plateau regions, and this is the first report of kidney biopsy data from children living in these regions. We found that there were differences in renal pathological types between children in plateau and non-plateau regions.

The most frequent histopathological group of kidney diseases is primary GN in children and adults.²⁻⁴ In our study, secondary glomerular disease was the most common renal pathology in plateau regions, which is different from previous results for adults from the Tibetan region.¹¹ The reason for this difference between studies remains unclear, but it may be related to a possible selection bias

or a lack of awareness of routine urine examinations. Most children do not visit a doctor until they have edema, gross hematuria, and high blood pressure.

The distribution of types of primary GN varies among centers.^{1,4,5,9,12-15} In our study, NS and hematuria were the most common indications for kidney biopsy, which is in accordance with other studies of children.^{13,16} IgAN is the most common primary GN worldwide.^{9,12,14,16,17} In our study, IgAN was also the most common pathological type of primary GN (41.56%) in the plateau group, in line with the results reported from most countries.^{9,12,14,16,17} Additionally, the proportion of IgAN in our study was much higher than that in adults from the Tibetan region.¹¹ Zhou et al.¹¹ reported that IgAN accounted for 5% of adult primary glomerular diseases in the Tibetan plateau region. MGA was another major pathology in our study population, consistent with results reported from Italy,⁹ Korea,¹² Spain,⁵ and the Czech Republic.³ However, the frequencies of MsGN and FSGS in our study were much lower than those previously reported in Korea,¹² Spain,⁵ and Brazil.¹⁸ The reasons for these differences among studies are

unclear, and they may be related to age, race, genetic background, and even environmental factors. FSGS lesions often occur first at the junction of the renal cortex and medulla. If the number of glomeruli obtained from a renal biopsy specimen is small or the specimen is not from the junction of the renal cortex and medulla, early FSGS diagnosis may be missed.

In secondary glomerular disease, purpura nephritis was the dominant pathology in both groups, which is consistent with previous results reported from China,^{4,19} Italy,⁹ Korea,¹² Croatia,^{4,19} and Turkey.¹³ In China, HBV-GN was the most common secondary glomerular disease in the 1980s and 1990s, resulting from vertical HBV infection from the mother to the neonate. In recent years, the incidence of HBV-GN has declined because of more widespread use of hepatitis B vaccines in neonates. However, in our study, the frequency of HBV-GN in plateau regions was still higher than that in non-plateau regions. This difference may be because children living in rural areas are not receiving regular hepatitis B vaccinations. The pathogenesis of systemic lupus erythematosus is related to environmental factors, especially exposure to ultraviolet radiation.²⁰ Previous studies have indicated that there are some differences in the incidence and clinical characteristics of LN at different altitudes and for different nationalities.^{21–23} Although plateau areas are exposed to strong ultraviolet radiation, the proportion of LN in the plateau group was significantly lower than that in the non-plateau group in this cohort. This result is similar to that in a study by Zhou et al.¹¹ These authors suggested that the proportion of adults with LN in plateau regions was significantly lower than that in non-plateau regions. Further studies are required to determine whether the causes are related to racial and environmental differences.

Our study has several limitations that should be noted. First, this was a

single-center study. The numbers of pathological types were relatively small and may not have been truly representative. Second, differences in renal pathological types found between children in plateau and non-plateau regions may be related to multiple factors, such as genetic or environmental factors, race, infection, renal biopsy indications, renal biopsy rates, and pathological renal examination methods. Some of the pathological types that we analyzed have a variable incidence among different races. Therefore, our conclusions may not be applicable to other plateau regions.

In conclusion, there are differences in renal pathological types between children from plateau regions and non-plateau regions. IgAN, as a primary GN pathology, and purpura nephritis, as a secondary GN pathology, are the most common kidney diseases among children in plateau regions. Despite this study's limitations, it may provide insight into the spectrum of pediatric kidney diseases in plateau regions.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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