Original Article

Histological pattern of paediatric renal diseases in Northern Pakistan

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Abstract

Objective: To determine histological spectrum of renal diseases among the paediatric population in the province Khyber Pukhtunkhwa, and to note any change in histological pattern with age and serum creatinine.

Methods: This is a retrospective analysis of 415 paediatric renal biopsies performed at the department of nephrology, Lady Reading Hospital Peshawar from 1998 - 2005. Children from 3 to 15 years of age, having renal disease and indications for biopsy, underwent ultrasound guided percutaneous renal biopsy. Indications included nephrotic syndrome, nephritic/nephrotic syndrome with renal insufficiency and nephrotic syndrome with steroid resistance.

Patients with acute or chronic renal failure were not included. The specimens were examined without immunoflorescence, under light microscopy using different staining techniques, Results were analyzed for different age groups, serum creatinine levels and for both male and females with renal disease.

Results: The overall male to female ratio in the study was 1.6: 1. Nephrotic syndrome was most common indication for renal biopsy in 50% of the cases, followed by renal insufficiency (26%) and steroid resistance (24%). In children with primary glomerulonephritis, minimal change disease (MCD) was found to be the most common histological pattern (24.09%), followed by focal segmental glomerulosclerosis (FSGS), 18.30%; mesangioproliferative glomerulonephritis (GN) (MsePGN), 17.83%; mesangiocapillary GN (MPGN), 11.08%; post streptococcal proliferative GN (Post. strep GN), 10.60%; membranous GN (MGN), 4.82%; crescentic GN (Cres.GN), 4.34%. Among children with secondary GN, chronic sclerosing GN was found to be most common (1.93%), followed by chronic tubulo interstitial nephritis (Chr.TIN), 1.69% and hypertensive nephropathy (H.Neph), 1.69%; Renal Amyloidosis, 0.96% and Lupus Nephritis III, 0.96%; acute tubular necrosis (ATN), 0.72%; Alport's Syndrome(0.48%)

Overall, MCD was the most common histological pattern in all age groups and among children with serum creatinine < 1.2mg/dl. However, that with serum creatinine between 1.3 to 3 mg/dl, MsePGN was found to be more common. Age turned out to be significant factor, in contrast to serum creatinine, in determining various histological patterns.

Conclusion: This study highlighted the histological patterns of renal disease among pediatric population from northern part of Pakistan. MCD was on the top followed by FSGS, but frequency of MCD was less than cited in earlier studies.

Keywords: Paediatric renal diseases, Minimal change disease, Nephrotic syndrome, Northern Pakistan (JPMA 61:653; 2011).

Introduction

In renal medicine, histological examination of renal tissue lays the foundation of clinical diagnosis due to which, kidney biopsy remains the chief diagnostic procedure in variety of nephritides. This procedure not only correlates the histological pattern of disease with the clinical outcomes but also helps to dictate the therapeutic options and forestalls prognosis. Interestingly, in renal medicine, histological descriptions are used to name clinical diseases or syndromes.

Percutaneous renal biopsies in children were first reported by Galan and Maso in 1957 in their study of nephrotic children.[1] The same year, Farquhar at al. published the first report of series of papers concerning paediatric renal biopsies.[2] Kidney biopsy in children is more challenging than its adult counterpart as it requires skillful handling of anxious young patients, in addition, to thorough counseling of worried parents about the need of this invasive procedure. However, with improvements in ultrasound technique and

availability of automated spring loaded guns, this procedure is considered safe in experienced hands.[3]

Although percutaneous renal biopsies in children have been reported in various studies in the past, no statistically significant data in this regard has been collected at our province with a population of 22 million in addition to 2.8 million Afghan refugees. In this scenario, our study takes into account a retrospective analysis of 415 paediatric biopsies performed over a period of 7 years from 1998 to 2005. These biopsies were performed on the basis of clinical indications and the results were analyzed for age, sex and different creatinine levels.

Subjects and Methods

All percutaneous renal biopsies were performed in children between 3 to 15 years of age with renal disease and indications for biopsies. Indications included nephrotic syndrome, nephritic/nephrotic syndrome with renal insufficiency and nephrotic syndrome with steroid resistance. Renal insufficiency was defined as having serum creatinine > 1.2 mg. Patients with nephrotic syndrome along with steroid resistance were considered as those having no response to steroids in therapeutic doses for 8 weeks. This by itself remained an indication of biopsy in about 24% of cases. Moreover, patients with acute or chronic renal failure were not included in this study. Children < 3 years of age were referred to Surgery department, for biopsy under general anaesthesia, and therefore, were not considered for analysis. Similarly patients with diabetes, history of nephrolithiasis, symptoms suggestive of acute renal injury, reflux nephropathy, family history of renal disease and renal transplant, were excluded from our study. Indications for biopsy included frequently relapsing nephrotic syndrome, primary steroid resistance, rapidly progressive nephrotic syndrome, haematuria, and proteinuria of varying degree with renal insufficiency. Steroid resistance is considered as no response to steroids after 8 weeks of adequate dosage whereas relapse of nephrotic syndrome more than 3 times in preceding 6 months or on dosage reduction is considered as frequently relapsing nephrotic syndrome.

Prior to performing the biopsy procedure, written consent was taken from each patient after giving a detailed video demonstration of the procedure in an audio - visual (AV) room. All the patients had their complete blood count (CBC), renal function tests (RFTs), haematocrit levels (HCT), autoimmune profile and hepatitis screening done before the procedure and no biopsy was considered in patients with HB% < 10 g/dl.

All biopsies were performed at the Department of Nephrology and Hypertension, Lady Reading Hospital (LRH), using 2% lidocaine. About 40% of the biopsies were performed using trucut biopsy needle (18 G × 150 mm) while the remaining were performed with the help of automated spring loaded monotopy gun (Bard Monotopy USA 18 G).

Kidney was localized with the help of Real Time Ultrasound machine and its lower outer quadrant was selected, in each case, for the purpose of biopsy. Two pieces of renal tissue were taken from each patient and were preserved in N/10 normal saline. These samples were then sent to Aga Khan Laboratories where they were examined under light microscopy using Haemotoxylin and Eosin (H and E), Periodic Acid Sciff (PAS), silver nitrate and Congo red staining methods.

WHO classification of kidney disease was employed and various histological patterns of renal disease were classified as minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), mesangioproliferative glomerulonephritis (MsePGN), mesangiocapillary glomerulonephritis (MPGN), post streptococcal proliferative glomerulonephritis (Post. strep GN), membranous glomerulonephritis (MGN), hypertensive nephropathy (H.Neph), crescentic glomerulonephritis (Cres.GN), chronic tubular interstitial necrosis (Chr.TIN), chronic sclerosing glomerulonephritis (GN), Alport's Syndrome, acute tubular necrosis (ATN), Lupus Nephritis III, Renal Amyloidosis, or Inconclusive.

The Chi - square (χ^2) test of independence was used to analyze the change in distribution of histological patterns with age, sex and serum creatinine levels. All results were calculated at 5% level of significance ($\alpha = 0.05$) and were considered statistically significant when $p < 0.05$.

Results

A total of 415 paediatric kidney biopsies were performed percutaneously from 1998 to 2005 with a success rate of 99.5%. Results were analyzed for both males and females of different age groups with varying levels of serum creatinine, across different histological patterns of renal disease. Out of 415 renal biopsies, 273 (65.8%) were performed in children between 11 to 15 years of age, 118

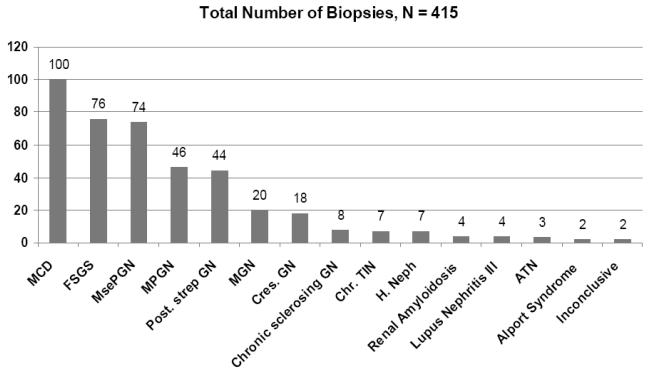

Figure-1: Frequency of various histological patterns of renal disease.

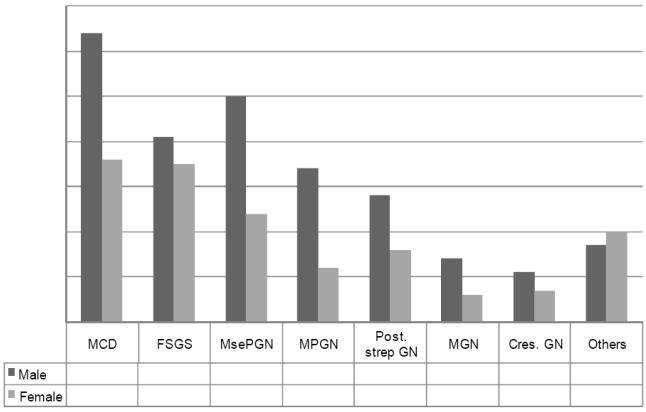

Figure-2: Male to Female ratio across various histological patterns.

(28.4%) were performed in children between 6 to 10 years of age, while remaining 24 (5.8%) biopsies were performed in children under 5 years of age.

The study involved 259 males and 163 females with an overall male to female ratio of 1.66 : 1. The ratio was highest among children under 5 years of age (5 : 1) and lowest among children between 6 to 10 years of age (1.2 : 1). However among children between 11 to 15 years of age, comprising the largest population in our study, the male to female ratio was 1.79: 1. Thus there was a statistically significant variation in male to female ratio across different age groups, p = 0.017. Nephrotic syndrome was found to be the most common indicator for renal biopsy in our region being present in 205 cases (50%), followed by renal insufficiency in 109 cases (26%) and steroid resistance in 101 cases (24%).

Overall, 378 (91.08%) children had primary glomerulonephritis (GN) where as only 37 (8.92%) children had secondary GN. Among the children with primary GN, MCD was found to be the most common histological pattern (24.1%), followed by FSGS (18.30%), MsePGN (17.83%), MPGN (11.08%), Post. strep GN (10.60%), MGN (4.82%) and Cres.GN (4.34%). Similarly, chronic sclerosing GN (1.93%), Chr.TIN (1.69%), H.Neph (1.69%), Renal Amyloidosis (0.96%), Lupus Nephritis III (0.96 %), ATN (0.72 %) and Alport's Syndrome (0.48%) were common among children with secondary GN (Figure-1).

However, due to large number of cases with primary GN, the histological pattern seen in primary GN, persisted making MCD as the overall most common histological pattern of renal disease in our population. Histological pattern remained inconclusive in only 2 cases (0.48%) due to insufficient specimen tissue, thus having only an insignificant effect on our study. Males predominated females in almost all histological patterns and there was no statistically significant variation in male to female ratio across different histological patterns of renal disease, p = < 0.154 (Figure-2).

Children between 11 to 15 years of age were more common than those of other age groups but there was significant variation between the age groups across different histological patterns of renal disease. Similarly, although MCD was the most common histological pattern among children in all age groups, there was statistically significant variation in the disease ratio across different age groups, p = 0.001. Thus age turned out to be a significant factor in determining histological pattern.

Likewise, children with serum creatinine levels between 0 to 1.2 mg/dl were more common than children with serum creatinine > 1.2mg/dL levels however, insignificant variation was present between different ranges of serum creatinine, in various histological patterns of renal disease. Therefore, in our study, serum creatinine turned out to be an insignificant marker in diagnosis of various histological patterns.

MCD was the most common histological pattern in children with serum creatinine levels between 0 to 1.2 mg/dl, which is good agreement with the results shown by other studies (Table). Whereas MsePGN was more predominant pattern among children with serum creatinine levels between 1.3 to 3 mg/dl. Again variation in the disease ratio across different ranges of serum creatinine levels was statistically insignificant, p = 0.069.

Table: Histological patterns of disease across different studies.

	MCD	FSGS	MsePGN	MPGN	MGN	Others
Present study (n = 415)	24.09%	18.30%	17.83%	11.08%	4.82%	23.88%
Churg et al. 1979 (n = 521) [From ISKDC, 1970][22]	76.40%	6.90%	2.30%	7.50%	1.50%	5.40%
White et al. 1970 (n = 145)[16]	77%	7.50%	5.50%	6%	1.50%	2.50%
Srivastava et al. 1975 (n = 206)[14]	77%	5%	5%	4%	1.50%	7.50%
Bonilla-Felix 1999 (n = 152)[15]	35%	31%	17.10%	3.30%		
Al Menawy et al. (1997)[23]	25%	14.80%	17.60%	10.20%		
al-Rasheed et al. 1996 (n = 167)[24]	23.30%	24%	24%	6.60%	4.80%	17.30%
Habib et al. (1971)[25]	51.50%	11.50%		1.30%	9%	

Discussion

Nephrotic syndrome has been documented as the most common cause of renal disease among pediatric population less than 15 years and majority of children suffering from different glomerular diseases present clinically as nephrotic syndrome.[4,5] However, with those having idiopathic nephrotic syndrome, majority have shown sensitivity to steroids with a response rate of 90 to 94%.[6,7]

In quest of elucidating the histological patterns of renal disease among pediatric population having indications for biopsy, a number of observational analysis have been conducted worldwide. Some of them have also tried to find the influence of different factors such as age, sex or type of patient on frequency of different histological pattern of renal disease.[8] In this regard, a number of studies have also been reported from Pakistan taking paediatric population under consideration and finding the most common histological pattern of renal disease among them.[9-12]

The main indicators for renal biopsy in these studies was steroid resistance, steroid dependence or atypical features. Most of these studies enrolled relatively small number of cases ranging from 30 to 43 patients, thus reducing the level of statistical significance. They have shown FSGS as the most common pattern of renal disease among children with steroid resistance. However, in one study, MsePGN has been cited as the most common pattern among children with steroid resistance.[11]

Recently a study, with a sample size of 538 cases, was reported from SIUT (Sindh Institute of Urology and Transplantation) showing that MCD and its variants (43.8%), FSGS (38.14%) and MGN (7.96%) remain the leading histological pattern of kidney disease in their population.[13] However no single study with appreciable sample size, to draw statistical conclusions, was available from our province. In this regard, our study takes into account 415 paediatric biopsies collected over a period of 7 years and analyzed retrospectively.

Our study showed nephrotic syndrome as the most common indicator for renal biopsy while MCD, which has been cited as the most common renal disease in children,[14-17] came out to be the most prevalent histological pattern in our population as well. Even among the patients with frequently relapsing nephrotic syndrome, MCD predominated the histological diagnosis. This was in contrast to our expectant diagnosis of FSGS as the dominant pattern among these patients. The reason lies in our socio-economic and cultural scenario. As in many of frequently relapsing nephrotic children, the parents would stop therapy after 6 weeks when the patient is oedema free, assuming that patient has responded and would recommence treatment only when the oedema becomes obvious. Hence, the patient would oscillate between partial remission and early relapse several times before coming to Nephrology care.

In our study, isolated haematuria alone was not considered as an indicator for biopsy due to which IgA Nephropathy was not documented in our study. Also non availability of immunoflorescence contributed to same. IgA Nephropathy has highest prevalence rates in Japan.[18] An Italian study, while considering isolated haematuria as the most common indicator for biopsy, not surprisingly has also shown IgA Nephropathy as the most common histological pattern.[8]

Table-1 shows the comparison of different histological patterns of renal disease in various studies. The comparison clearly shows MCD as the most prevalent histological pattern in all studies. Some studies in this comparison have also considered variations among different age groups across various histological patterns. International Study of Kidney Disease in Children (ISKDC 1978) had documented that of children diagnosed with nephrotic syndrome, 78.6 % of those with MCD while 50% of those with FSGS were < 6 years of age.[6] This was in contrast to our study where majority of children with MCD and FSGS were between 11 to 15 years of age. Likewise in our study, only 4% of children with MCD and 2% of children with MsePGN had serum creatinine > 3 mg/dl. This was again in contrast to (ISKDC 1978), where 32.5 % of patients with MCD and 40.6% of patients with MsePGN had raised serum creatinine.[6]

Only 7 out of the 415 patients analyzed had hypertensive changes. Three of them had features of chronic sclerosis. However, only two had changes of chronic TIN in addition to features of hypertensive nephropathy. The cause of hypertensive nephropathy could not be ascertained in two cases.

Similarly, ATN was seen only in 3 patients and all of them had aggressive diuretic therapy as a part of their treatment for nephrotic syndrome.

Not a single case of HUS was recorded as most of these (HUS) cases are diagnosed on the basis of clinical history and laboratory findings of microangiopathic haemolytic anaemia, thrombocytopenia and raised LDH. Since the main aim of this study was to find the histological pattern of nephrotic syndrome, HUS which presents as acute renal failure was not included in this study.

Likewise, Alport Syndrome was seen in only 2 cases and both of them were diagnosed on the basis of positive family history, positive findings of sensory neural deafness and ocular abnormalities along with suggestive histopathological picture. Electron microscopy (EM) was not performed in either of these cases.

Similarly, Lupus was seen only in 3 cases and

diagnosis was based on serology and positive findings for focal proliferative GN, characteristic of Type III Lupus.

Studies have reported the use of Pethidine and Medazolam for the purpose of sedation in paediatric renal biopsy.[19] At our hospital, no patient had complication due to the biopsy procedure, keeping the fact that all biopsies were performed under local anaesthesia and without using any sedation. Hence, we feel that local anaesthesia using 2% lidocaine is sufficient for performing paediatric renal biopsy in experienced hands.

Our study had some limitation of non availability of immunoflorescence facility during the study period. However, it still remains an important clinical question, whether the availability of this diagnostic procedure has any effect on frequency of various histological diagnosis and their management in our study. We consider the clinical features and the course of disease in addition to lab and light microscopy findings sufficient for clinical diagnosis, which is in good agreement with an Indian study,[20] except in nephritides such as pauci-immune glomerulonephritis, systemic lupus erythematosis (SLE), IgA / IgM nephropathy and anti-GBM (glomerular basement membrane) mediated glomerulonephritis. Interestingly in our study, except for IgA / IgM nephropathy, which would have made a good percentage of MsePGN, all the other nephritides mentioned were not common in our population and therefore would have had only a little or no influence on the frequency of various histological patterns.

In this regard, data from another good study conducted at SIUT,[21] was analyzed for renal biopsies using Light Microscopy, Immunoflourescence and Electron Microscopy over a period of 12 years. Even with availability of the above diagnostic facilities, the percentage of patients with MCD (29.4%) and FSGS (21.8%) did not differ significantly from the percentage of cases seen in our study.

Conclusion

This study has shown MCD as the most common histological pattern of renal disease among paediatric population which is in agreement with other studies. However, MCD was seen to occur with decreasing frequency in our population in contrast to earlier studies. FSGS has come up to be the second most common cause of frequently relapsing nephrotic syndrome and steroid resistance in our population. Similarly, Mesangio Prolif GN and Post. strep GN, though relatively uncommon in the west, were high on the merit of histological diagnosis.

The histological pattern seen in our study (Northern Pakistan) is comparable to the studies conducted at SIUT (Southern Pakistan). Interestingly, despite the non availability of Immunoflourescence, histological disease pattern did not change!

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