Original Article

Atypical Nephrotic Syndrome

Histopathologic and Clinicopathologic Correlations in Children with Atypical Nephrotic Syndrome

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ABSTRACT

Objective: To find histopathologic and clinicopathologic correlations in children with atypically presented nephrotic syndrome.

Study Design: Retrospective observational study

Place and Duration of Study: This study was carried out at the Department of Paediatric Nephrology, Children's Hospital & Institute of Child Health, Multan, Pakistan **f**rom December, 2005 to January, 2014.

Materials and Methods: Medical record and the biopsy reports of 80 children (age 1-15 years) with nephrotic syndrome, who had atypical features at presentation and had a renal biopsy, were analyzed. Atypical features included hypertension, gross hematuria, hypocomplementemia, impaired renal function, and age more than 12 years, or manifestation of other systemic diseases in children.

Results: Overall results showed hypertension as the commonest (90%) atypical feature followed by impaired renal function (65%), atypical age (53.7%), gross hematuria (41.3%), and hypocomplementemia (31.3%). Histopathologic reports revealed non-MCD lesions in 76 (95%) cases. The commonest lesion was FSGS (25%) followed by MesPGN (23.8%), MCGN (17.5%), and LN (12.5%). Out of the total 80 patients, 62 were idiopathic atypical nephrotic syndrome cases and 18 were secondary (due to some underlying systemic cause) nephrotic syndrome cases. Secondary causes, in decreasing frequency, included lupus nephritis/nephrosis (LN) (n=10; 55.5 %), hepatitis B virus associated nephrosis (HBVAN) (n=4; 22.2%), Henoch Schonlein Purpra nephritis/nephrosis (HSPN) (n=2; 11.1%), hepatitis C virus associated nephrosis (HCVAN) (n=1; 05.5%), renal amyloidosis (RA) (n=1; 05.5%).

Conclusion: Renal biopsy done at the onset of atypically presented nephrotic syndrome provides useful guidance to the final diagnosis. Non-MCD lesions predominate. Some secondary nephrotic syndrome patients also present as atypical nephrotic syndrome; further clinical and laboratory evaluation reveals the secondary cause.

Key Words: Atypical nephrotic syndrome, secondary nephrotic syndrome, children, renal biopsy.

INTRODUCTION

Nephrotic syndrome in children is the most common renal disease with median age at presentation of 4 years. It is characterized by heavy urinary protein losses. Typical cases of nephrotic syndrome are mostly (> 90%) steroid responsive with minimal change disease being the commonest histopathology (~ 80%).[1] Therefore, these children are started on steroids without recourse to renal biopsy. However, renal biopsy may be indicated in children who present clinically with nephrotic syndrome and who also have some atypical features which may indicate other unusual underlying histopathologial lesions or systemic diseases that affect the kidneys.[2-6] These atypical cases may require specific management protocols and other supportive care. The atypical features may include age less than 12 months or greater than 12 years, persistent hypertension, impaired renal function, gross hematuria, hypocomlementemia (low C3), or presence of extra renal clinical manifestations.[1,5] There is limited data about histopathological variants in nephrotic children and adolescents who present with atypical features and those with underlying systemic diseases. Available results also show changing trends of histopathological lesions.[7-13]

The Children's Hospital and the Institute of Child Health, Multan, Pakistan is a tertiary care referral hospital draining pediatric patients from a wide population area. Nephrotic syndrome is one of the commonest renal diseases being referred to this hospital for detailed evaluation. The present study was designed to elucidate the spectrum of underlying glomerular lesions in the atypically presenting nephrotics with primary renal disease or with any underlying secondary cause and also to evaluate the clinicopathologic correlations in these patients.

MATERIALS AND METHODS

In this observational retrospective analysis, medical record of 80 nephrotic children, who had one or more atypical features at presentation, was reviewed. These children were biopsied between December, 2005 to January, 2014. The inclusion criteria were nephrotic syndrome with one or more atypical features at disease onset which include age $\geq$ than 12 years, gross hematuria, persistent hypertension, deranged renal function tests, decreased C3 level, or extrarenal

systemic disease manifestations. Congenital (age < 3 months) or infantile onset (age < 1 year) nephrotic syndrome cases were excluded because these may be hereditary, syndromic or due to congenital infections. Also, the patients with typical acute post-streptococal glomerulonephritis and those with any absolute contraindication to renal biopsy were excluded. For the purpose of this study nephrotic syndrome was defined as massive proteinuria of > 40mg/m^2/hour or spot urinary protein-creatinine ratio >2(mg:mg), presence of edema, and serum albumin <2.5g/dl. Gross hematuria was defined as urine grossly red or cola colored with RBCs field full or numerous on microscopy. Hypertension was labeled when systolic and/or diastolic blood pressure was persistently $\geq$ 95th centile for age, gender and height on 3 separate readings. Hypocomplementemia was taken as C3 level less than age specific lower limit (< 77mg/dl for age 1-10 years and <83mg/dl for age more than 10 years). Impaired renal function was defined as serum creatinine more than the upper limit of normal for age. Age $\geq$ 12 years was considered an atypical feature in this study.

In the prepared patients, ultrasound guided percutaneous renal biopsy was performed with Dr. J Fine Core Disposable Semiautomatic Biopsy Needle (size 16 G x 150 mm) under local anaesthesia. Two to three cores of renal tissue were taken. Biopsy specimen, preserved in formalin, were sent to the histopathologist at Dr. Zia-ud-Din University Hospital, Karachi for histopathological review by light microscopy (LM) and immunofluorescence (IF) study.

Patients' name, age, date of admission, registration number, presenting complaints, details of history and physical examination, related laboratory tests and biopsy indications and results were obtained by a careful review of the record and the biopsy reports. The atypical features and the outcome variable, that is histopathological lesions, were noted.

Data was analyzed using statistical software SPSS-19. Descriptive statistics were applied to analyze the data. The quantitative variables were calculated by mean and standard deviation and qualitative variables by percentages and frequencies. Various crosstabulations were used to evaluate the clinicopathologic correlations.

RESULTS

In the present study a total of 80 patients, who were biopsied due to atypical nephrotic syndrome, were included. Mean age was 10.94 $\pm$ 2.82 years with an age range of 4 to 15 years. Age at presentation was highest in the age group 12 to 15 years (n=43; 53.7%) with a mode of 13 years. There were 23 (28.7%) patients in the age group 8 to 11 years and 14 (17.5%) patients in the age group 4 to 7 years. No atypical nephrotic syndrome patient was seen between 1 to 4 years age. Sex- wise break-up showed 50 (62.5%) males and 30 (37.5%) females with a male to female ratio of 1.7.(Table I).

Table No.I: Demographic characteristics of patients (N=80)

Age Group (Years)	Male	Female	Total
1-4	00	00	00
>4-7	10 (12.5%)	4(5%)	14(17.5%)
>7-11	14 (17.5%)	9(11.25%)	23(28.75%)
>11-15	26(32.5%)	17(21.25%)	43(53.75%)
Total	50(62.5%)	30(37.5%)	80(100%)

Table No.2: Correlation between histopathological lesions and atypical features.

Histopathological Lesion	Gross Hematuria	Low C3	Hypertension	Impaired Renal Function
FSGS (N=20)	01 (05%)	01 (05%)	19 (95%)	15 (75%)
MesPGN (N=19)	08 (42.1%)	02 (10.5%)	16 (84.2%)	08 (42.1%)
MCGN (N=14)	09 (64.3%)	09 (64.3%)	13 (92.9%)	12 (85.7%)
LN (N=10)	07 (70%)	10 (100%)	10 (100%)	08 (80%)
MGN (N=05)	00	00	04 (80%)	04 (40%)
MCD (N=04)	00	00	03 (75%)	00
CGN (N=04)	04 (100%)	03 (75%)	04 (100%)	04 (100%)
HSPN (N=02)	02 (100%)	00	02 (100%)	02 (100%)
IgAN (N=01)	01 (100%)	00	00	00
RA (N=01)	01 (100%)	00	01 (100%)	01 (100%)

Key: FSGS= Focal Segmental Glomerulosclerosis, MesPGN= Mesangioproliferative GN, MCGN= Mesangiocapillary GN, LN= Lupus Nephritis, MGN= Membranous GN, MCD= Minimal Change Disease,CGN= Crescentic GN, HSPN= Henoch Schonlein Purpra Nephritis, IgAN= IgA nephropathy, RA= Renal Amyloidosis

Renal biopsy reports showed focal segmental glomerulosclerosis (FSGS) as the most common lesion (N=20; 25%) followed by mesangioproliferative glomerulonephritis (MesPGN)(N=19; 23.8%), mesangiocapillary glomerulonephritis (MCGN)(N=14; 17.5%), lupus nephritis (LN)(N=10; 12.5% [08 had

diffuse proliferative LN and 02 had membranous LN]), membranous glomerulonephritis (MGN)(N=5; 6.3%), crescentic glomerulonephritis (CGN)(N=4; 05%) and minimal change disease (MCD) (N=4; 05%). Two patients of Henoch Schonlein Purpura nephritis (HSPN) with associated nephrotic state showed diffuse mesangial proliferation with crescentic GN.

One patient showed IgA nephropathy (IgAN) and another had renal amyloidosis (RA) detected on biopsy. Distribution of atypical features showed that seventy two (90%) patients had persistent hypertension, fifty two(65%) patients had impaired renal function at presentation, 33(41.3%) had gross hematuria, and hypocomplementemia (low C3) was present in 25(31.3%) patients. Clinicopathologic correlation between different atypical features and histopathologic lesions is given in table 2.

Table No.3: Causes of secondary nephrotic syndrome presenting as atypical nephrotic syndrome (N=18).

Causes	No. of patients	Positive serology	Histopathology
LN	10	Low C3, Low C4, anti dsDNA	DPGN(N=08), MGN(N=02)
HBVAN	04	HBsAg, HBV DNA(PCR)	MN(N=03), MesPGN(IgMN)
HSPN	02		MesPGN+CGN
HCVAN	01	anti HCV, HCV RNA (PCR)	MCGN
RA	01	RAF	RA

Key: LN= Lupus Nephrosis/Nephritis, HBVAN= Hepatitis B Virus Associated Nephrosis, HSPN= Henoch Schonlein Purpra Nephrosis/ Nephritis, HCVAN= Hepatitis C Virus Associated Nephrosis, RA= Renal Amyloidosis, anti dsDNA= anti double-stranded DNA antibody, RAF= Rheumatoid Arthritis Factor, DPGN= Diffuse Proliferative Glomerulonephritis(WHO class IV), MGN= Membranous Glomerulonephritis(WHO class V), MN= Membranous Nephropathy, MesPGN(IgMN)= Mesangioproliferative Glomerulonephritis with IgM nephropathy, CGN= Crescentic Glomerulonephritis, MCGN= Mesangiocapillary Glomerulonephritis

Eighteen (37.5%) patients had clinical or laboratory manifestation of other systemic diseases upon further evaluation. Ten patients (12.5% of total patients) had positive antinuclear antibody (ANA), low C3, low C4, and raised anti-double stranded DNA (dsDNA) antibodies; these were all cases of Lupus nephritis/nephrosis (LN) and renal biopsy showed diffuse proliferative LN in 8 patients and membranous LN in 2 patients. Four patients (05% of total patients) were Australia antigen (HBsAg) positive and HBV DNA by PCR (polymerase chain reaction) was also detected in blood; these proved to be hepatitis B nephritis/nephrosis and renal biopsy had supportive features (membranous nephropathy in 3, and mild mesangial proliferation with IgM nephropathy in one patient). One patient had positive anti-hepatitis C (anti HCV) antibody and HCV RNA was detected by PCR showing active viral replication; renal biopsy revealed MCGN secondary to HCV infection. Liver function tests were normal in these hepatitis B an C positive cases. (Table 3).

DISCUSSION

Atypical presentation amongst nephrotic syndrome cases in children and adolescents is not an uncommon occurrence.[11,12] The atypical features may include atypical age (<12 months and $\geq$ 12 years), hypertension, deranged renal function, gross hematuria, low complement[3], or some extra renal clinical manifestations of a systemic illness which may present with secondary nephrotic syndrome.[1,5] These patients are mostly steroid resistant and are associated with a high risk of developing chronic kidney disease. Hence, renal biopsy is required for diagnosis and specific treatment.[2-4] The incidence of various histopathological subtypes in atypically presented nephrotic syndrome varies from the typical idiopathic nephrotic syndrome and reports from around the world show changing trends.[7-14] Garg AK et al[14] in a study in 2009 in India on clinicopathological spectrum of renal biopsy in children showed that the commonest renal pathology in atypical nephrotic syndrome was MesPGN (38%) followed by MCD(18.2%) and FSGS(14.4%). They biopsied 51 out of 85 children with nephrotic syndrome at onset because of atypical presentaion. A study by Ejaz I et al[16] at King Edward Medical college, Mayo Hospital, Lahore, Pakistan in 2001 showed FSGS 42%, MCD 22%, MCGN(MPGN) 14% and MesPGN 12%. The indications for biopsy in these patients were atypical presentation, initial or late steroid resistance, or steroid dependant patients relapsing on <1mg/kg/day prednisolone. On presentation, 40% had hematuria, 20% were hypertensive, 12% had renal insufficiency, and in 4% C3 was low. A study at Sindh Institute of Urology and Transplantation, Karachi, Pakistan showed an increasing prevalence of FSGS over the years in Pakistani population with higher prevalence of atypical features.[7] A study done at Chittagong, Bangladesh by Mehmud NU et el[17] showed that in atypically presented nephrotic syndrome in children, there was male predominance with a M:F of 1.7. The most common atypical feature was atypical age (55.9%) followed by hematuria (13.6%), hypertension (10.2%), and low C3 level (1.7%). They took age < 2 years and > 8 years as atypical. We decided to include atypical age spectrum to < 1 year and $\geq$12 years because many patients between 1-2 years and between 8-12 years may present with no other atypical feature and may also be steroid responsive. Hence, undue renal biopsies were avoided. However, the biopsy was performed in these borderline

age group patients later on if they did not respond to steroid therapy. In another study done at Bangabandhu Sheikh Mujib Medical University, Dhaka by Begum A et al[12], in 40 children with atypical nephrotic syndrome, hypertension, gross hematuria, impaired renal function, and hypocomplementemia were observed in 50%, 45%, 19%, and 15% cases respectively. Histopathology revealed that 90% cases had lesions other than MCD. The results of our study also indicate that nephrotic children and adolescents presenting with atypical features are very likely to have histopathological lesions other than MCD, as only 4 patients out of the total 80 had MCD. It also showed that more the number of atypical features in any individual patient, more the chances of non-MCD glomerular lesion or some secondary cause of nephrotic syndrome. MesPGN was the commonest lesion (47.5%) in their study but it was the second commonest lesion in our study. The majority (56.8%) of their atypically presented nephrotic syndrome were resistant to steroid therapy. Gooden M et al[11] in 2010, in Jamaica, West Indies also showed that MesPGN was the commonest (31.2%) histology in atypical nephrotic syndrome. In our study, majority of patients had two or more atypical features at the first presentation. Overall, hypertension was the most frequent atypical feature followed by impaired renal function and atypical age. Persistent high blood pressure was present in the vast majority of atypical nephrotic patients in all the histopathological subtypes. Except for patients with MCD, most of the patients with other glomerular lesions had impaired renal function at presentation. Patients in the age group of 12-15 years had the highest number of atypical features. Also, the number of patients in this age group .was significantly higher than younger age groups (P value< 0.05). Sex predilection was female in cases of LN (8/10) and male in all other categories. This might be explained by the higher number of male patients in our study. Overall, gross hematuria was seen most frequently in patients with MCGN (27.3%), followed by MesPGN (24.2%), and LN (21.2%). It was also seen in all patients with CGN, HSP, IgAN and RA. As expected, hypocomplementemia was present in all patients with LN, 9/14 (64.3%) in patients with MCGN, and 3/4 (75%) patients with CGN. Hypocomplementemia in two patients with MesPGN and one patient with FSGS was unexplained.

Our study also included 18 patients with secondary nephrotic syndrome because their initial presentation was as atypical nephrotic syndrome but further clinical and laboratory evaluation done due to atypical features revealed the final diagnosis of secondary nephrotic syndrome. Ten patients were diagnosed to have lupus nephrosis with low C3 and C4, and positive anti dsDNA antibodies. Out of these 10 patients, 8 had diffuse proliferative LN (WHO class IV), and 2 showed membranous LN (WHO class V) on renal biopsy. Hafeez F et al[18] in a case series of LN in 26 children showed that diffuse proliferative LN was the commonest lesion (n=14), followed by membranous nephropathy (n=6). In their study, the commonest clinical manifestation was edema (80.76%) followed by hypertension (46.15%), hematuria (38.46%), and azotemia (19.33%). Proteinuria was present in 100% cases with nephrotic range proteinuria seen more commonly in WHO class III and IV. The results of an Italian Collaborative Study of lupus nephritis in children and adolescents showed that many patients have only renal disease at onset and lack sufficient criteria to diagnose SLE clearly.[19] Our LN patients also presented initially as nephrotic syndrome with some atypical features; but after further laboratory and clinical evaluation, they proved to be cases of SLE. In our study, Hepatitis B and C nephroses were detected because we routinely screen all the nephrotic patients for HBsAg and anti-HCV antibody status as a prerequisite before starting induction with steroids because there is risk of HBV or HCV reactivation with steroids. Positive cases on screening tests are confirmed with either ELISA (Enzyme Linked Immunosorbent Assay) or ECI (enhanced chemi-illuminescence). With normal liver function tests and positive immunoassay tests, the patients are further requested for PCR test. If PCR detects active viral replication, these patients are subjected to renal biopsy. Biopsies consistent with HBV and HCV associated nephritides are the candidates for specific anti-viral or interferon therapy. Many studies from around the world have shown that hepatitis B virus (HBV) may induce extrahepatic lesions in different organs. HBV associated glomeulonephritis is one of the more important extrahepatic diseases and nephrotic syndrome is its most common clinical manifestation.[20-22] According to these studies,the most common pathology is membranous nephropathy ; other lesions may be minimal change nephropathy, MesPGN, MPGN, and IgAN.[23,24] IgM nephropathy is rare but it was seen in one of our 4 patients; the rest 3 had MGN. One patient in our study proved to have hepatitis C virus (HCV) associated MCGN which manifested as nephrotic syndrome. Other studies favour such presentation.[25] Two patients with HSPN and one each with IgAN and RA had nephrotic proportion proteinuria at presentation. These are the rare cases with such presentation and have
poor prognosis.[26-29] Our study combined primary atypical nephrotic syndrome cases with some secondary nephrotic syndrome patients who also presented as atypical nephrotic syndrome. It was after further evaluation that the secondary cause could be elucidated.

CONCLUSION

Vast majority of atypically presented nephrotic syndrome in children and adolescents had

histopathological lesions other than minimal change disease which is the commonest lesion in typical cases of nephrotic syndrome. Some atypically presented cases finally proved out to be secondary to systemic underlying cause. Renal biopsy at the onset of atypical nephrotic syndrome is very helpful to the final diagnosis.

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