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Influence of disease remission on renal dimensions in childhood nephrotic syndrome in Ibadan, South West Nigeria

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Abstract*:* *Background:* The hallmark of Nephrotic syndrome is massive proteinuria, with associated enlarged kidneys. However the association between remission status and size of the kidneys in patients with nephrotic syndrome is not known. This study is aimed at determining the dimensions of the kidneys of children with nephrotic syndrome and to compare kidney dimensions in patients with nephrotic syndrome who were in remission compared with the dimensions in patients who were not in remission.
Subjects and Methods: This is a case-control study, where fifty-three children with diagnosis of Nephrotic syndrome and fifty-seven age matched healthy controls were analysed. The kidneys of both cases and controls were scanned using the B- mode ultrasound and the kidneys Bipolar, anteroposterior and transverse dimensions and volume were determined.
Results: The mean renal longitudinal, anteroposterior, transverse dimensions and volume were higher in cases compared to the controls, bilaterally ($p < 0.001$). The mean difference in values of the measured parameters between the cases in remission and those yet to attain remission was not significant. The bipolar dimension of the left kidney showed positive correlation with duration of disease ($r = 0.290$, $p = 0.035$). The study was also able to demonstrate high incidence of nephromegaly, in 52.8%, 62.3% and 67.9% respectively for the right kidney, left kidney and combined.
Conclusion: Despite a comparative global enlargement in the kidney dimensions in children with nephrotic syndrome compared with controls and the general population, the remission status does not seem to be a significant factor.

Keywords: Nephrotic syndrome, renal dimensions, ultrasonography, nephromegaly, paediatric.

Introduction

Nephrotic syndrome is a leading cause of chronic renal disease, with subsequent morbidity and mortality among the paediatric age group.[1–5]It is defined by the presence of massive proteinuria, hypoalbuminaemia, and anasarca.[3] It is thus technically defined as defined as the presence of nephrotic- range proteinuria (>40mg/m^2/hr), or urine protein to creatinine ratio of >2-3mg/mg, hypoalbuminaemia (<2.5-3.0g/dl) and oedema.[3]
There is usually an associated nephromegaly.[6]
Proteinuria being a major yardstick in nephrotic syndrome, its absence would also signify disease resolution. This is termed remission, which is dipstix proteinuria of <1+ for three consecutive days.[7] Thus, attaining remission is an important goal in the management of the disease.[7]

Despite a series of publications emphasizing the renal enlargement seen in nephrotic syndrome,[6,8] however little is known about the relationship of the renal enlargement and disease remission.
Ultrasonography is a recognised investigative tool in assessing the kidneys of the patients with nephrotic syndrome, especially the renal size. Ultrasound is also important as an adjunct procedure to localize the kidneys when performing renal biopsy.[9]

Materials and methods

This is a prospective study

Ethical approval was obtained from the University of Ibadan / University College Hospital ethical review committee, as the study spanned through twelve months (July 2013 to July 2014).
Fifty- five cases with known diagnosis of nephrotic syndrome were recruitedfrom the Children emergency ward and Children outpatient clinic of the University College

Hospital, Ibadan. Two were eventually dropped because they defaulted and could not be traced. Fifty- seven healthy controls were also recruited to give a total of one hundred and twelve subjects for the study. The control subjects were children of members of staff and friends.
Every consecutive child, whose parents consented to the study, was recruited. These cases met the diagnostic criteria (Nephrotic-range proteinuria of >40mg/m^2/hr, or Urinary protein to Creatinine ratio of >2, hypoalbuminaemia of <2.5g/dl and oedema).[3,10]The average age of the NS cases was 126.24 ± 40.11months, with a majority (56.6%) in the 10 – 15yearsage brackets. The mean age of the control subjects is slightly lower ((117.63± 38.11months).

Complete remission was defined as protein negative or trace on urine dipstick for 3 consecutive days while relapse was defined as proteinuria of ≥ 3+ on urine dipstick for 3 consecutive days. Infrequent relapse was defined as one relapse within 6 months of initial response, or one to three relapses in any 12-month period. Frequent relapse was two or more relapses within 6 months of initial response, or four or more relapses in any 12-month period. Steroid dependent nephrotic syndrome referred to two consecutive relapses during corticosteroid therapy, or within 14 days of ceasing therapy. Steroid sensitive nephrotic syndrome included patients who achieved remission with steroid therapy and had not recordedany relapse as well as infrequent relapsers, frequent relapser and patients with steroid dependent nephrotic syndrome.[7]Steroid sensitive nephrotic syndrome included infrequent relapsers, frequent relapsers and steroid dependent nephrotic syndrome. Steroid resistance was defined as failure to achieve complete remission after 8 weeks of corticosteroid therapy.[7]
Patients with nephrotic syndrome were initially managed with per oral (p.o) prednisolone 60mg/m^{2}daily for 4-6 weeks and 40mg/m^2/day for 2-4 weeks to make at least 8 weeks of prednisolone therapy.
Patients who attained remission went on to receive 4 additional months of tapering doses of p.o prednisolone in the initial episode.[6]While first relapse of nephrotic syndrome and infrequent relapsers were managed with p.o prednisolone 60mg/m^2 until remission and 40mg/m^2 on alternate day for 4 weeks.[7]Steroid resistant nephrotic syndrome was usually managed with monthly intravenous (i.v) Cyclophosphamide (2mg/kg/d) for 6 months, p.o prednisolone, and angiotensin converting enzyme inhibitors.[7]

A consent form was filled and signed by the parents of the proposed subjects. Likewise, a verbal assent was also obtained from each child old enough to do same.
The kidneys of the cases, as well as that of the age-matched controlswere scanned. The control group had urinalysis to rule out any subclinical proteinuria. They were also screened by the B mode ultrasound to ensure they had normal parenchymal echogenicity and preserved corticomedullary differentiation, so as to exclude those with abnormal parenchymal echogenicity. These were done in the department of Radiology by the Radiologist.
The ultrasound low frequency (2-5KHz) transducer of Mindray M7, 2010 by Shenzhen Mindray bio- medical electronics company limited ultrasound machine was used. The subjects were scanned in supine, lateral oblique and prone positions.
The kidney sizes were measured in centimetres while the subject lied in prone position, as the measurements were taken from the back. The renal dimensions (Bipolar length, Width, Thickness and Volume) were derived by using the in-built electronic callipers of the machine. The callipers were placed at the edges of the kidneys in craniocaudal, anteroposterior, and transverse planes to estimate the bipolar length, thickness and width respectively of the kidneys. The measurements were standardized for consistency. To obtain the bipolar length, the upper and lower poles of the kidney were marked and the maximal value obtained at the midsagittal plane. The anteroposterior dimension was also obtained from the same midsagittal image. The transverse scan was obtained perpendicular to the axis of the midsagittal plane, and measurement for the transverse dimension made at about 1cm point from the hilum. Each subject was scanned once. No variability expected, as ultrasound was done by single Radiologist. The renal volume was derived by the machine's in-built algorithm, using the ellipsoid formula (Bipolar length(LS) x breadth (AP) x width (TS) x 0.523).[11]

The presence of nephromegaly was determined by comparing the kidney sizes of each of the cases with age and sex matched population from a previous study.[12]
Statistical Analysis was done with SPSS version 17. The mean value ± standard deviation of the kidney dimensions (Length, breadth, width, and volume), were depicted in tables. The mean renal dimensions in cases and controls as well as in those in remissions versus those who were not in remission were compared by independent student t- test.
The correlation between disease duration and renal dimensions in the nephrotic cases were determined by Pearson's correlation.

Results

A total of One hundred and twelve children were recruited for the study, out of which fifty- five (49.1%) were the primary cases with nephrotic syndrome and the remaining fifty- seven (50.9%) were controls. However, two of the recruited cases were dropped from analysis due to incomplete data as they were lost to follow up.
The age and sex distribution of the cases and healthy controls were demonstrated in table 1. The subjects were predominantly males in both the cases and control group. Thirty- two (60.4%) of the analyzed cases were male, while there were thirty- four (59.6%) males among the controls. The average age of the cases was 126.24 ± 40.11months. The mean age of the controls is slightly lower (117.63± 38.11months). The mean difference in age between the cases and control group was not statistically significant (p= 0.44). The mean ages of the

cases in remission and those not in remission were 118.6months and 125.3months respectively. This is also of no statistical significance (p= 0.61)
The duration of illness ranged from 1week to 87months (7.25years) with a mean of 20.29monthsand most of the cases (71.7%) hadduration of illness less than 2years (Table 2).

Table 1: Age and sex distribution of the cases and controls

	Nephrotic cases (n=53)	Controls (n=57)
Age (months)		
Males	122.2 ± 39.9(p= 0.78)	114.0 ± 37.4(p= 0.40)
Female	125.6 ± 45.3	123.0 ± 39.3
Sex		
Males	32 (60.4%)	34 (59.6%)
Females	21 (39.6%)	23 (40.4%)

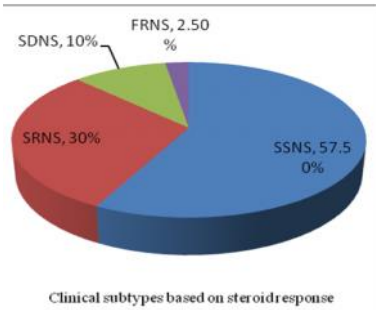
No statistical significance between mean ages of the cases and controls (p=0.44)

Table 2: Duration of disease in the cases

Duration (months)	Number	%
<2years	38	71.7
2-<4years	6	11.3
4- < 6years	5	9.4
≥ 6years	4	7.5

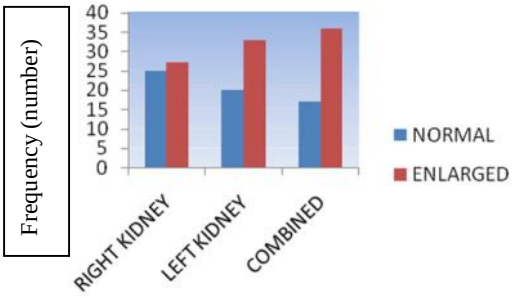
Forty of the fifty- three of the recruited cases were classified based on response to steroid therapy. The other children are still within the 4- 8weeks steroid trial, thus they could not be classified. However, of the classified cases, majority (37, 70%) were steroid sensitive nephrotic syndrome as shown in figure 1.

Fig 1: 3D pie chart showing the clinical classification of the children with nephrotic syndrome based on the response to steroid therapy. Majority of the cases were of the steroid sensitive (SSNS) subtype, while the least occurring subtype is the FRNS.



Only about one-fourth (14, 26,4%) of the cases were in remission, as at the time of this study. The remaining (39, 73.6%)were either in relapse or yet to attain remission. A high occurrence of relapse was also reported in 27 (67.5%) of the cases. A third (14, 35%) of which also demonstrated proteinuria level of 3+.
There is a high prevalence of nephromegaly in the cases. This is demonstrated by more than a half (28, 52.8%), almost two-thirds (33, 62.3%), more than two-thirds (36, 67.9%) respectively by the right kidney, left kidney and combined (figure 2).

Fig 2: A column showing a higher number of the cases demonstrating nephromegaly



The mean LS, AP and TS dimensions in the cases were significantly greater than in the control subjects (p< 0.001) (Table 3).In addition, the left kidney was generally larger in its mean LS, AP and TS dimensions in both the cases and controls.

Table 3: Comparison of the dimensions of both kidneys for the cases and controls

Measured parameters	Cases Mean ± sd	Controls Mean ± sd	T	p- Value
Right kidney				
Longitudinal	9.82 ± 1.23	8.30 ± 1.05	6.785	<0.001
Anteroposterior	4.39 ± 0.85	3.66 ± 0.42	5.558	<0.001
Transverse	4.45 ± 0.77	3.69 ± 0.42	6.301	<0.001
Volume	102.32± 45.72	56.05 ± 16.15	6.829	<0.001
Left kidney				
Longitudinal	10.28 ± 1.53	8.60 ± 1.88	6.205	<0.001
Anteroposterior	4.75 ± 0.84	3.71 ± 0.46	7.720	<0.001
Transverse	4.88 ± 0.97	3.95 ± 0.46	6.170	<0.001
Volume	126.66± 56.67	63.53± 21.39	7.407	<0.001

p value <0.05 is significant

However, the comparison of the mean values of the renal dimensions of the children who were not in remission and those in remission only showed marginal, but non-significant increase in the LS, AP and TS dimensions, as well as volume of both kidneys in the former. (Table 4).

Table 4: Comparision of the mean kidney dimensions in the nephrotic children in remission and those not in remission

Parameters measured	In remission	Not in Remission	T	P Value
RK- Bipolar Length	9.59 ± 1.34	9.87 ± 1.22	0.667	0.513
RK- Anteroposterior	4.12 ± 0.91	4.47 ± 0.81	1.230	0.234
RK- Transverse	4.24 ± 0.60	4.52 ± 0.80	1.333	0.193
RK- Volume	90. 76 ± 51.54	105.21 ± 43.52	0.909	0.375
LK- Bipolar Length	10.01 ± 1.92	10.34 ± 1.41	0.549	0.589
LK- Anteroposterior	4.52 ± 1.00	4.80 ± 0.79	0.948	0.355
LK- Transverse	4.74 ± 1.10	4.91 ± 0.94	0.511	0.615
LK- Volume	120.05 ± 76.18	127.12 ± 49.55	0.324	0.750

Mean (in cm), Volume (in cm^3), RK is Right kidney, LK is Left kidney.

The duration of disease showed significant positive correlation with the bipolar dimension of the left kidney only (r= 0.290) (p= 0.035). Thus, the longer the duration of disease, the longer the bipolar length, as shown in table 5.

Table 5: Relationship between the duration of disease and dimensions of both kidneys in the cases

Measured parameters	Right kidney		Left kidney	
	R	p- Value	R	p- Value
Longitudinal	0.141	0.317	0.290	0.035
Anteroposterior	-0.065	0.645	0.074	0.600
Transverse	-0.064	0.650	0.091	0.519
Volume	-0.046	0.744	0.153	0.275

p <0.05 is significant, r = Pearson's correlation

Discussion

The mean age of the children with nephrotic syndrome in this study is higher than that from other regions where mean ages of 5.3 years and 3.8years in Kuwait and Saudi Arabia have been reported.[13,14] This may be due to geographic factors.

The relative low rate of patients in remission is in contrast to the high occurrence in Enugu (63.9%)[15] and Benin city (51.7%)[16] in Nigeria, as well as in Kuwait (84%)[13] and in Finland (82.5%)[17]. This is probably also due to the rarity of minimal change disease in our environment[18] and also difference ethnic genetic makeup.

Despite the relative low remission rate in the cases, quite a high proportion was classified as steroid sensitive. The low proportion of patients in remission may also be due to high relapse rate at the time of this study as it was documented in previous local studies. Anochie et al[19] (in Port Harcourt) and Ibadin et al[16] (in Benin) reported an initial steroid response of 80% and 51.7%, with subsequent high relapse of 75% and 43.4% respectively. Asinobi et al[20] in Ibadan also reported an initial steroid response of 60%. Olowu et al[21,22] in Ile- Ife also reported initial remission of 57.1% and 64.1% in separate publications, yet with a high relapse of 64.1% in the initially sensitive patients. A high incidence (46.3%) of steroid resistance was also documented. Similarly, Nammarlwar et al[9] also reported a high incidence (65.2%) of steroid resistance among the Indian children.

There is presence of nephromegaly, just as reported in a previous study by Gersen et al in the United States where 42% of the paediatric cases demonstrated nephromegaly.[8]

There was a trend toward a higher kidney dimensions in nephrotic syndrome patients who were not in remission compared to values in patients who were in remission. In addition, a comparison of renal dimensions in the different remission statuses is also difficult due to non-availability of previous publications. Larger studies are however needed to confirm the finding that remission status does not significantly influence the size of the kidneys in patients with nephrotic syndrome. A search through the literature also revealed paucity of studies on the association between duration of nephrotic syndrome and kidney dimensions.

Conclusion

A comparative global enlargement of all the renal dimensions in nephrotic syndrome was confirmed by this study. There was a trend towards larger mean bipolar, anteroposterior and transverse kidney dimensions in nephrotic syndrome patients who were not in remission as compared with patients who were, but the difference was not significant. Larger studies are however needed to confirm influence of disease remission status on renal dimensions. This may per- haps be able to demonstrate serial kidney dimensions as an adjunct to urinary protein in assessing disease remission.

Conflict of interest: None
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