Renal Sonographic Findings in Nigerian Pre- School Children with Asymptomatic Proteinuria

* Dr. Odutola Israel Odetunde	Dr. Adesina Olalekan Semiu Aderibigbe	Dr. Ngozi Rosemary Njeze
Paediatric Nephrology Unit, Department of Paediatrics, University of Nigeria Teaching Hospital, Ituku Ozalla, Enugu, Enugu State, Nigeria. * Corresponding Author	Department of Radiation Medicine, University of Nigeria Teaching Hospital, Ituku Ozalla, Enugu, PMB 01129, Ituku-Ozalla, Enugu State, Nigeria	Department of Radiation Medicine, University of Nigeria Teaching Hospital, Ituku Ozalla, Enugu, PMB 01129, Ituku-Ozalla, Enugu State, Nigeria

Dr. Kingley Ihedioha Achigbu	Dr. Josephat Maduabuchi Chinawa
Department of Pediatric, Federal Medical Centre, Owerri, Imo State , Nigeria.	Pediatric Cardiology Unit, Department of Pediatrics, University of Nigeria Teaching Hospital, UNTH, Ituku Ozalla, Enugu. PMB 01129, Ituku- Ozalla, Enugu State, Nigeria.

Dr. Oluwatoyin arinola Odetunde	Prof. Henrietta Uche Okafor
Pediatric Surgery Unit, Department of Surgery, Enugu State University Teaching Hospital, Enugu, Nigeria.	Pediatric Nephrology Unit, Department of Pediatrics, University of Nigeria Teaching Hospital, UNTH, Ituku Ozalla, Enugu. PMB 01129, Ituku-Ozalla, Enugu State.

ABSTRACT *Background: We carried out this study to evaluate the usefulness of ultrasonography in the early detection of renal disorder in pre- school children with asymptomatic proteinuria. Method: A multi- stage interval early morning urinalysis was carried out on the subjects (before and after) renal ultrasound examination for persistent proteinuria.*

Result: There was a prevalence of 2.7% (17 subjects) for proteinuria at the first screening with no age or gender preponderance (P value > 0.05). Persistent proteinuria (urinalysis done after two weeks) was found to be 1.6% (10 subjects). Three subjects (30 %) with persistent proteinuria had abnormal renal ultrasonographic findings. Second interval urinalysis, 4 months after the first urinalysis revealed unremitting proteinuria in 2 subjects (66.7%) and1 (14.3%) of the subjects with abnormal and normal renal ultrasonographic findings respectively. Conclusion: Persistent proteinuria may be early feature of renal disorder, hence it is desirable to evaluate such subject starting with ultrasound and interval urinalysis in order to make early detection of the disease.

Background

Renal disease in children detected by urine screening and follow -up evaluation had better prognosis when compared with those presenting with massive proteinuria. Studies have shown a decline in the incidence of end stage renal failure (ESRF) in children with chronic glomerulonephritis since the introduction of urinary mass screening in Japan [1, 2].

The finding of at least two positive urine tests out of three specimens would suggest persistent proteinuria and warrants a proper evaluation. Asymptomatic proteinuria poses diagnostic dilemma. However, evidence relating renal disorders to asymptomatic proteinuria has been demonstrated [3-5] and since most renal diseases are chronic in nature asymptomatic proteinuria may be an early manifestation of the disease. Evaluation of a child having persistent asymptomatic proteinuria should include renal ultrasonography to evaluate the kidney outline, size, parenchymal structure and vessels in addition to other investigation like a urine culture, measurement of creatinine clearance, Spot urine protein /creatinine ratio, determination of serum albumin and C_3 complement level.

Renal ultrasonography is very important in evaluating a child with persistent asymptomatic proteinuria, especially where invasive diagnostic procedure like urography and renal bi- opsy cannot be carried out to establish the renal pathology [6-8]. Investigating   a child's kidney and urinary tract should almost always start with an ultrasound especially in the asymptomatic phase of the disorder. The examination is independent of renal function and provides anatomical details of the kidney and urinary tract as well as other retroperitoneal and intra- abdominal structures. This investigation includes measurement of renal length which is important in assessing kidney growth. Normal grow h charts are available for age, weight, height, and should be used routinely as a reference tool [9, 10]. This study was carried out to evaluate sonographical findings of pre- school children with asymptomatic persistent proteinuria in the early detection of renal disorder.

Methods

Setting and study design

A stratified method of sampling was used to select subjects from registered nursery schools in the three local Government Areas (LGA) within Enugu metropolis with pre- school population of about 37,556 (7% of total population) [11]. Approval was obtained from The Ethical committee of the University of Nigeria Teaching Hospital (UNTH) and the State Ministry of Education before the commencement of the study. Written informed consent was obtained from the parents or the caregivers of the subjects before being enrolled into the study. A frame of nursery schools was constructed

for each of the LGA and four schools were randomly selected systematically. The selected schools were used to form strata in which the subjects were selected.

Selection of schools and subjects was influenced by the co-operation and readiness of the management to participate in the research.

Six hundred and thirty (n = 630) subjects gave their informed consent to be part of the study and also met the inclusion criteria of relatively healthy children, age between 2 and 5 years old (at the last birthday), absence of symptoms of renal disease like dysuria, increase urinary frequency or urgency, macroscopic hematuria and facial or pedal edema, absence of fever a week prior to the study, and parental or guardian consent.

Children with confounding and modifying factors of proteinuria such as fever, intense activity or exercise, dehydration, emotional stress were excluded from the study.   This was achieved by thorough history taking and physical examination.

A screening urinalysis, using the reagent strip Medi-Combi 10 test strips manufactured by Machery-Nagel D-52313 Duren, Germany, was done on early morning urine for proteinuria. The proteinuria was graded as follows + (30mg/dl); ++ (30 to 100mg/dl); +++ (100 to 300mg/dl); ++++ (1000mg/dl and above). Proteinuria of 1 + or more were accepted as significant. Subjects with significant proteinuria had a repeat urinalysis two weeks after the first urinalysis to detect persistent proteinuria. Subjects with persistent proteinuria were followed up subsequently and invited further evaluation with renal ultrasound to estimate the renal size and this was compare it with normal size for age, the echotexture of the parenchyma and the corticomedullary differentiation. Spot urinary protein: creatinine ratio {UrP/Ucr }, serum creatinine for estimated Glomerular Filtration Rate (eGFR) calculation using the modified Schwartz formula [12] were obtained within 2-4 weeks of the first proteinuria positive urinalysis in the laboratory of the university of Nigeria teaching Hospital. All subjects with persistent proteinuria were given 4months appointment for repeat interval urinalysis to check for unremitted proteinuria.

Statistical analysis
Data analysis was done using statistical package for social sciences (S.P.S.S for windows 17.0 output). Descriptive statistics analysed for percentile values, central tendency and dispersion. Frequencies were compared using Chi squared test. Data presentation was in tables and charts.

Results
Out of 1400 pupils selected for the study, 630 subjects obtained informed consent to be part of the study and also met the inclusion criteria of the study. The age and gender distribution of the subjects is as shown in Table 1. Seventeen (2.7%) of the subjects had varying degree of proteinuria. The proteinuria cut across all the age and gender groups, Table 2. Repeat urinalysis in the17 subjects with proteinuria at 2weeks followed -up visit revealed persistent proteinuria in 10 subjects (1.6%), 4(0.6%) had negative proteinuria and 3(0.5%) subjects dropped-out of the study and   actually defaulted from follow-up visit.

Renal ultrasound in the subjects with persistent proteinuria (n = 10) revealed normal renal size and echotexure in all subjects and poor corticomedullary differentiation in three (30 %) of the subjects. (Table 3)

The Minimum value of 0.8 for UrP/Ucr and the maximum value of 2.1 with mean of 1.2 ±0.39. Only 1(0.16%) of studied subjects had UrP/Ucr in the nephrotic range. (Tables 3)

eGFR value obtained ranged from 64 – 106 ml/min/1.73m³

with mean of 78.7 ml/min/1.7m³ $\pm$ 12.6 ml/min/1.7m³, in the subjects with persistent proteinuria. (Table 3)

Three subjects (30%) of the 10 subjects with persistent proteinuria had unremitted proteinuria with interval urinalysis done at 4 months after the first urinalysis giving a prevalence of unremitted proteinuria to be 0.5% of the studied subjects. While 2 (66.7%) of the 3subjects with abnormal ultrasonographic findings had unremitted proteinuria, 1(14.3%) of 7 subjects with normal renal ultrasonographic findings also had unremitted proteinuria (Figure 1). Subjects with unremitted proteinuria with or without abnormal ultrasonic findings were referred to paediatric nephrology clinic, University of Nigeria Teaching Hospital for follow- up. All the subjects with unremitted proteinuria declined to renal biopsy.

Discussion
Most chronic renal disorders have the asymptomatic phase of urinary abnormality with persistent proteinuria preceding the overt phase of the disease. Asymptomatic Proteinuria especially when persistent and unremitted deserves special emphasis because they are hallmark of possible significant renal disorder. Among the plethora of indications for imaging of the renal tract, the guiding principle in paediatric nephrology should be to choose the least invasive technique with the lowest radiation dose and work up only as necessary to the most invasive technique and higher radiation burden. This study focused on the pre – school age children being the age group before the peak age of renal disorder in Enugu where this study was carried-out with a peak between five and seven years of age [13,14].

In this study the prevalence of proteinuria was found to be 2.7 %, 1.6% and 0.5% for persistent and unremitted proteinuria respectively. This compares favourably with the findings of Vehaskari and Rapola [15] and Dodge et al [16] where two to four samples were tested per child. The frequency of proteinuria fell following repeated testing of the initially positive individuals. In a study of 8, 954 school children in Finland proteinuria was detected in one of four specimens in 10.7 percent of the children and in at least two of four specimens in 2.5 percent of the children. In both genders the prevalence of proteinuria increased with age. Most children who had proteinuria on initial evaluation turned out to lose the proteinuria at follow–up. Only about 10 percent of children have persistent proteinuria after six to 12 months of follow up [17, 18].

The renal ultrasound finding in the subjects with persistent proteinuria revealed poor corticomedullary differentiation in three (30 percent) of these subjects. The sonographic depiction of echogenic cortex relative to hypoechoic kidney pyramids is referred to as corticomedullary differentiation. Normal corticomedullary differentiation is important because absence of this feature although nonspecific, may be indicative of underlying renal parenchymal disease. Sixty – seven percent of subjects with abnormal ultrasonographic findings had unremitted proteinuria compare to the 14% in subjects with normal ultrasonographic finding. The 14% of the subjects although without renal ultrasonographic findings had UrP/Ucr value in the nephrotic range. The eGFR of all the subjects with persistent proteinuria was greater than 60ml/min/1.73m². The current evaluation, classification and stratification system described by the National Kidney Foundation, Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines defined Chronic Kidney Disease (CKD) as the presence of markers of kidney damage like proteinuria for ≥3 months with evidence of structural and functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR) that is manifested by either pathological abnormalities or other markers of kidney damage, including abnormalities in the blood, urine or in imaging tests or GFR <60 mls/min/1.73 m² for ≥3 months, with or without kidney damage [19, 20]. Three of our studied subjects had abnormal ultrasonographric findings, two of which had unremitted proteinuria at 4months. It can be extrapolated that 3subjects had asymptomatic early stage of CKD, giving a prevalence of 0.5% of the studied subjects.

Persistent proteinuria, abnormal renal ultrasonographic findings and unremitted proteinuria deserve special emphasis for hallmarks of possible significant chronic renal parenchymal disorder and should be further evaluated and followed-up.

Renal ultrasonography is very important in evaluating a child with persistent asymptomatic proteinuria, especially in situation where invasive diagnostic procedure like urography and renal biopsy cannot be carried out to establish the renal pathology [6-8]. Children who require uroimaging for whatever reason should undergo full ultrasound examination first. In order to establish renal pathology, especially in an asymptomatic subjects, in an environment where consent for renal biopsy is not readily given, radiological studies such as ultrasonogram can be of use.

The limitation of this study is the decline of renal biopsy (which would have been the ultimate in determining the present of actual nephropathy) by the subject with unremitted proteinuria. The parents of these "symptom-less children simply refused to be convinced that their wards would from any invasive tests. Caregivers of some of the subjects that were positive for the primary screening, feeling "they were not sick", could not be persuaded for further investigation and were lost to follow up.

Conclusion

We conclude that asymptomatic, persistent and unremitted proteinuria could be a presumptive evidence of an underlying renal parenchymal disease and they should be properly investigated and followed – up. Inevitably all children with asymptomatic presumptive evidence of renal disease should start with a renal ultrasound examination. Ultrasound is noninvasive, independent of renal function and should be available in all nephrology units as a basic radiological investigation.

TABLE I :-AGE AND GENDER DISTRIBUTION OF SUBJECTS.

AGE (YEARS)	MALE n (%)	FEMALE n (%)	TOTAL n(%)
2	66 (19.1)	50 (17.5)	116 (18.4)
3	85 (24.7)	84 (29.5)	169 (26.8)
4	95 (27.5)	68 (23.9)	163 (25.9)
5	99 (28.7)	83 (29.1)	182 (28.9)
TOTAL	345 (100)	285 (100)	630 (100)

$\chi^2 = 2.40$ df = 3   P = 0.49

TABLE 2: AGE AND GENDER DISTRIBUTION OF SUBJECTS WITH PROTEINURIA.

| AGE (YEARS) | PROTEINURIA | | | |
	- ve n (%)	+ ve n (%)	++ ve n (%)	TOTAL n (%)
2	111 (17.6)	5 (0.8)	0 (0)	116 (18.4)
3	166 (26.3)	3 (0.5)	0 (0)	169 (26.8)
4	159 (25.2)	3 (0.5)	1 (0.2)	163 (25.9)
5	177 (28.1)	5 (0.8)	0 (0)	182 (28.9)
TOTAL	613 (97.3)	16 (2.5)	1 (0.2)	630 (100)

$\chi^2 = 5.08$ df = 6   p = 0.53

GENDER				
MALE	339 (53.8)	5 (0.8)	1 (0.2)	345 (54.8)
FEMALE	274 (43.5)	11 (1.7)	0 (0)	285 (45.2)
TOTAL	613 (97.3)	16 (2.5)	1 (0.2)	630 (100)

$\chi^2 = 4.47$ df = 2   P = 0.12

TABLE 3: ESTIMATED GFR, UrP/Ucr, SONOGRAPHIC FINDINDS AND UNREMITTED PROTEINURIA IN SUBJECTS WITH PERSISTENT PROTEINURIA

IDENTIFICATION n=10(S/N)	UrP/Ucr (g/dl)	eGFR (ml/min/1.73m²)	RENAL SIZE	ECHOTEXTURE	CORTICOMEDULLARY DIFFERENTIATION	UNREMITTED PROTEINURIA
1(10)	0.80	75.0	NORMAL	NORMAL	NORMAL	NEGATIVE
2(43)	1.08	72.0	NORMAL	NORMAL	POOR	NEGATIVE
3(57)	1.52	64.0	NORMAL	NORMAL	NORMAL	NEGATIVE
4(120)	1.60	64.0	NORMAL	NORMAL	POOR	POSITIVE
5(139)	2.11	106.0	NORMAL	NORMAL	NORMAL	POSITIVE
6(182)	1.22	84.0	NORMAL	NORMAL	NORMAL	NEGATIVE
7(210)	0.94	88.5	NORMAL	NORMAL	NORMAL	NEGATIVE
8(223)	1.01	67.0	NORMAL	NORMAL	POOR	POSITIVE
9(247)	1.07	77.0	NORMAL	NORMAL	NORMAL	NEGATIVE
10(435)	1.12	85.0	NORMAL	NORMAL	NORMAL	NEGATIVE

FIGURE 1: THE TRENDS OF PROTEINURIA IN SUBJECTS

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