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The Clinical Parameters Affecting the Health-Related Quality of Life of Children with Nephrotic Syndrome

Ngozi Rita Mbanefo, Odutola Israel Odetunde*, Henrietta Uchenna Okafor, Tagbo Oguonu Anthony Nnaemaka Ikefuna, Agozie C Ubesie, Kenechukwu K Iloh, Adaeze Chikaodinaka Ayuk

Department of Paediatrics, College of Medicine, University of Nigeria and University of Nigeria Teaching Hospital Ituku Ozalla, Enugu, Nigeria.

odetoyintola@yahoo.co.uk

***Corresponding Author:** Dr. OI Odetunde, Pediatric Nephrology Unit, Department of Pediatrics, University of Nigeria Teaching Hospital, PMB 01129, Enugu 400001, Nigeria.*

Abstract

Introduction: *Nephrotic syndrome is a common chronic kidney disease of childhood whose characteristics can significantly affect the health-related quality of life (HRQoL) of affected individuals. It is the most common renal disorder requiring admission and accounts for about 40% of all renal disorders in our setting. The aim of this study is to assess the quality of life of children with nephrotic syndrome and to determine those factors that adversely affect it.*

Methods: *It was a descriptive cross sectional study of only children with nephrotic syndrome. The health-related quality of life of eligible children was assessed with PedsQL™ 4.0 Scale Score. Data obtained for physical, emotional, social and school domains were analyzed using the Statistical Package for Social Sciences (SPSS) version 19.0.*

Results: *Fifty children aged 5-18 years, 33 (66%) males and 17 (34%) females with nephrotic syndrome were recruited over a period of about one year. The mean ± SD for total scale of subjects without oedema, negative proteinuria, steroid sensitive and Minimal Change Nephrotic Syndrome histopathology (MCNS) are 81.26 ± 13.17, 84.78± 10.17, 80.98± 13.36 and 87.19 ± 6.72 respectively. While that of subjects with oedema, highest degree of proteinuria, steroid resistance and cytotoxic therapy and non-MCNS are 69.48 ± 11.21(t = 2.87, p = 0.0006), 65.58 ± 11.63(t = 7.76, p =0.001), 73.64 ± 12.17(t = 1.89, p = 0.066), and 74.82 ± 12.82(t= 2.70, p = 0.012). Subjects with duration of illness ≤ a year have means ± SD total scale score of 74.01 ± 13.39 and that of subjects with illness duration ≥ one year is 79.38 ± 13.62(t = 1.16, p = 0.25).*

Conclusion: *The HRQoL of children with nephrotic syndrome is worse with presence of oedema, disease severity (massive proteinuria, steroid resistance, non-MCNS histology type, cytotoxic therapy).*

Keywords: *Nephrotic syndrome, Quality of Life, Health- related Quality of Life, Children*

Introduction

Quality of Life (QoL) is the degree to which a person enjoys the important possibilities of his or her life.[1] QoL borders on who one is, how one is connected to one's environment, and whether one achieves one's personal goals, hopes, and aspirations [1]. The use of quality of life in the assessment of the state of the individual is referred to as QoL. When used in medical practice as Health related quality of life (HRQoL), it refers to the individual's wellbeing as it is impacted over time by a disease, disability, or disorder [2]. The impact that could be physical or psychological (emotional, social, school performance) is the reason for patients to seek medical consultation, and can be assessed using HRQoL scales. The scores obtained from those scales could help in predicting clinical outcomes with regards to morbidity and mortality.

Compromised HRQoL among patients with renal disease is well documented in the literature [3-6] with evidence of QoL impairments in children with CKD [5-8] and ESRD on renal replacement therapy [9-12]. In developed countries, some studies [2, 13-16] have also demonstrated a negative impact of nephrotic syndrome on the QoL of affected children. The factors associated with worse scores include steroid dependence [2, 17], steroid resistance [13-14], being on cytotoxic therapy [2,16], having frequent relapse [2, 16-17], disease severity [2, 14, 16, 17], as well as poor socioeconomic state and having a longer duration of illness [2, 13, 16, 17]. In developing countries, there is a dearth of literature on HRQoL of children with Nephrotic Syndrome (NS). The available studies focused on chronic diseases like asthma [18-19], cerebral palsy [20], and epilepsy [21]. This study therefore aims to assess the HRQoL of children with NS and the possible predictors of poor scores. Addressing identified needs during patient care will help improve clinical outcome and ultimately QoL.

Materials and Methods

Study Area and Site

The study was conducted at the University of Nigeria Teaching Hospital, which is located 23 kilometers from Enugu the capital of Enugu state in the southeast of Nigeria. The hospital is a tertiary hospital and a referral centre in the southeast, Nigeria. The hospital provides specialized nephrology care and has a designated pediatric nephrology clinic. An average of five children with nephrotic syndrome were seen weekly for follow up visits and about six new cases per year. There were 64 children diagnosed with NS on follow up in the clinic at the commencement of the study.

Inclusion and Exclusion Criteria

Children who were aged five to 18 years and previously diagnosed with nephrotic syndrome, whose parents or caregiver gave consent, were included in the study. Assent was also obtained from children older than 7 years. Children with co-existing medical, psychiatric, or cognitive impairment or other chronic medical conditions that can also affect QoL scores were excluded.

Patient Enrollment

Study participants who were previously diagnosed with Nephrotic syndrome were recruited based on their clinical and laboratory information as documented in the hospital medical records. Children who had a combination of the presence or history of generalized oedema, massive proteinuria with 3+ or 4+ of protein on urinalysis by dipstick [22, 23], spot urine protein creatinine ratio greater than 2g/24h/1.73m^2 or serum albumin less than 25g/L [22, 23], hypercholesterolaemia with serum cholesterol greater than 5.2mmol/L [22, 23], and or a kidney biopsy confirming histology subtypes of NS were classified as cases of Nephrotic syndrome. The clinical history of the subjects with regards to duration of illness, specific laboratory results, and medications were also obtained from the medical records.

Administration of the Questionnaire

The validated and age appropriate version of PedsQL 4.0, a generic questionnaire was interviewer-administered to children aged five to ten years. The questionnaire was self-administered for those children aged between eleven and 18years. The parameters on the questionnaire were scored on a five point Likert scale from zero (representing never) to four (almost always) for children aged eight to 18 years. For children aged five to seven years, a three point Likert scale was applied: zero (representing not at all), two (sometimes), and four (A lot of the times). The completed questionnaires were assessed for data entry. The scores were generated according to the developer's scoring system[24] and were then reversed and linearly transformed to a 0-100 scale where 0=100, 1=75, 2=50, 3=25, 4=0. Higher scores indicate better HRQoL while low scores indicate poorer HRQoL.

Data Management and Analysis

Information obtained was sorted, coded, and entered into the Statistical Package for Social Sciences (SPSS) version 19.0. Descriptive statistics were used to summarize quantitative variables (such as age) and qualitative variables (such as socioeconomic class). Differences between continuous variables were tested with Student t-test, ANOVA and a Duncan multiple comparison post-hoc test. Association between categorical variables was tested using chi square. All analyses were done at the 5% level of significance and *p*-value less than 0.05 was considered statistically significant.

Results

There were a total of fifty children as the study subjects, 33 (66%) were males and 17 (34%) females. The mean and median age was 6 and 7 years respectively, of which 20(40%) were aged 5-9 years age and 30 (60%) were aged 10-18years. A total of 17 (34%) children were in complete remission during the time of the study and defined as those with complete resolution (negative or trace by dipstick) of proteinuria for at least three consecutive days. Out of the 17 affected children, 3 (6%) were not on any medications, 6 (12%) were on calcineurin inhibitors while 8 (16%) were on steroids.

Children with partial remission defined as those with a reduction in the degree of the proteinuria to a non nephrotic range (1+ to 2+) were 21 (42%) in number. Five (10%) of these children were on calcineurin inhibitors while 16 (32%) were on steroid therapy. For those not in remission and with nephrotic range proteinuria, 3 (6%) were newly diagnosed, 4 (8%) were those who relapsed and 5 (10%) were those with steroid resistant but due to financial constraints were yet to commence other treatment modalities

Out of 50 children with nephrotic syndrome recruited for the study, 13 (26%) had edema while 37 (74%) children had no edema. Table 1 shows that the presence of edema significantly lowered the physical scale score (66.35 ± 19.65, p = 0.001), school scale score (46.54 ± 14.77, p = 0.002) and total scale scores (69.48 ± 11.21, p = 0.006) in affected children.

Table 1. *Differences between means PedsQL scale scores and the presence of oedema among children with nephrotic syndrome.*

Oedema				
Scale scores	Yes n (%) 13 (26) Mean ± SD	No n (%) 37 (74) Mean ± SD	t	p- value
Physical	66.35 ± 19.65	85.14 ± 14.68	3.627	0.001
Emotional	79.23 ± 23.79	79.73 ± 26.01	0.061	0.952
Social	87.69 ± 14.09	93.51 ± 10.33	1.586	0.119
School	46.54 ± 14.77	64.32 ± 17.64	3.250	0.002
Total	69.48 ± 11.21	81.26 ± 13.17	2.874	0.006

Seventeen (34%) subjects were in remission, 12 (24%) had 2+ of proteinuria, 12 (24%) had 3+ of proteinuria while 9 (18%) had 1+ of proteinuria. The physical, social, school and total scores were significantly lower in subjects with 3+ of proteinuria than in those with lesser degree of proteinuria ($F = 8.288$ $p < 0.001$, $F = 4.377$ $p = 0.009$, $F = 12.815$ $p < 0.001$, $F = 7.760$ $p < 0.001$ respectively). (Table 2)

Table 2. *Differences between mean PedsQL scale score among varying degrees of proteinuria in children with nephrotic syndrome*

Proteinuria						
Scale scores	Nil n (%) 17 (34%) Mean ± SD	1+ n (%) 9 (18%) Mean ± SD	2+ n (%) 12 (24%) Mean ± SD	3+ n (%) 12 (24%) Mean ± SD	F	p-value
Physical	89.24 ± 13.52	89.24 ± 13.45	79.43 ± 13.75	62.76 ± 18.58*	8.288	< 0.001
Emotional	87.35 ± 24.57	72.78 ± 21.95	75.42 ± 24.91	77.92 ± 28.79	0.877	0.460
Social	95.59 ± 7.68	97.22 ± 5.65	92.08 ± 10.76	82.92 ± 15.44*	4.377	0.009
School	65.59 ± 12.10	76.67 ± 15.81	57.92 ± 15.44*	40.42 ± 14.22*	12.815	< 0.001
Total	84.78 ± 10.17	84.66 ± 11.31	76.63 ± 13.03	65.58 ± 11.63*	7.760	< 0.001

*Duncan multiple comparisons indicating mean is significantly different from the rest

Thirty (60%) children were sensitive to steroid therapy while 20 (40%) were steroid-resistant. The mean emotional domain score (65.75 ± 23.58) of those who were steroid resistant was significantly lower (p = 0.002) when compared with those who were steroid sensitive (88.75 ± 22.61). However, scores in the remaining domains were lower in subjects who were steroid resistant, no significant difference was seen. Table 3

Table 3. *Differences of mean PedsQL scale scores between subjects who were steroid-resistant and those who were steroid sensitive*

	Steroid-resistance	Steroid-sensitive		
Scale scores	n (%) 30 (60) Mean ± SD	n (%) 20 (40%) Mean ± SD	t	p- value
Physical	77.97 ± 13.32	82.03 ± 20.77	0.754	0.455
Emotional	65.75 ± 23.58	88.75 ± 22.61	3.295	0.002
Social	89.50 ± 12.76	93.54 ± 11.08	1.124	0.267
School-functioning	58.75 ± 16.69	58.96 ± 19.78	0.037	0.970
Total	73.64 ± 12.17	80.98 ± 13.36	1.888	0.066

Fifty children with nephrotic syndrome, 27 (54%) had renal biopsy while 23 (46%) did not. Out of those who had renal biopsy, nine (18%) had the minimal change histology type while 18 (36%) had the non-minimal variant. The mean emotional score (62.78 ± 24.15) of subjects with non-MCNS was significantly lower (t = 4.272, p < 0.001) than that of patients with MCNS (97.78 ± 4.41). Also, the total score (74.82 ± 12.82) of those with the non-MCNS was also significantly lower (p = 0.012) than those with the MCNS (87.19 ± 6.72). Table 4

Table 4. *Differences of mean PedsQL scale scores between children with MCNS and those with non-MCNS.*

	Histology type			
Scale scores	MCNS n (%) 9 (18%) Mean ± SD	non-MCNS n (%) 18 (36%) Mean ± SD	t	p- value
Physical	88.89 ± 11.59	81.59 ± 14.49	1.310	0.202
Emotional	97.78 ± 4.41	62.78 ± 24.15	4.272	< 0.001
Social	95.56 ± 9.17	91.39 ± 13.04	0.855	0.401
School-functioning	65.56 ± 9.82	59.44 ± 17.65	0.961	0.346
Total	87.19 ± 6.72	74.82 ± 12.82	2.698	0.012

Table 5 shows the comparison of mean PedsQL scores between subjects whose duration of illness was within 12 months and those who had the disease for more than one year. The mean physical domain score of those whose duration of illness was less than one year was significantly lower (p = 0.002) than those whose duration of illness was more than one year. Also, the mean emotional score (93.64 ± 7.78) of those whose duration of illness was less than one year was significantly higher (p = 0.035) than those whose duration of illness was more than a year (75.64 ± 27.03). None of the other domains was significantly affected by duration of illness.

Table 5. *Differences of mean PedsQL scale score based on duration of illness*

Duration of illness				
Scale scores	≤ 1 year n (%) 11 (22%) Mean ± SD	>1 year n (%) 39 (78%) Mean ± SD	t	p- value
Physical	65.63 ± 24.33	84.38 ± 13.43	3.367	0.002
Emotional	93.64 ± 7.78	75.64 ± 27.03	2.168	0.035
Social	89.55 ± 10.11	92.69 ± 11.97	0.794	0.431
School-functioning	52.27 ± 17.94	61.79 ± 18.41	1.523	0.134
Total	74.01 ± 13.39	79.38 ± 13.62	1.158	0.253

Discussion

The presence of edema, massive proteinuria, steroid resistance and non-MCNS histology type were all observed in this study to have negative impact on HRQoL scores. In correlation with report from other studies, their effects on HRQoL are consistent irrespective of the patient population and instrument used [14,16, 17] Children with edema had poorer scores in the physical, school and total functioning domains. They were found to be unable to run and carry out routine daily physical activities. This effect on physical functioning could be attributed to limit mobility and fatigue cause by the disease symptoms. Gipson et al documented similar findings in their study [15]. Parental or caregiver anxiety may also play a role, as the affected child may not be allowed to engage in any play activity with their mates. In addition, presence of edema is a marker of disease activity and often distorts physical appearance. Therefore, parents/caregivers would prefer to take the affected child to hospital rather than to school. Frequent visits and or admission in hospital lead to more school hours being lost and resultant poor scores in school domain. A similar finding was reported by Manju *et al* who suggested that poor disease control evidenced by persistent of symptoms was responsible for poor school functioning [25]. The degree of impact of edema on HRQoL measures could explain the poor scores in the total functioning.

Varying degrees of proteinuria significantly affected the HRQoL scores. The greater the degree of proteinuria in the children, the more the impact on HRQoL with resultant low scale score recorded. Virtually all the domains were affected in children with 3+ of proteinuria. There was no significant difference in scores between children in remission and those with 1+ proteinuria. The reason for this finding could be that children with 3+ of proteinuria are likely to develop symptoms especially edema which has been found to impact negatively on HRQoL [14,16].

Subjects who had Steroid-resistant (SRNS) had poorer scores in the emotional domain than those who were steroid-sensitive. For patients who fail to achieve remission on steroid therapy, immunosuppressive therapy was commenced [26] and it is far more expensive than steroid therapy [27]. Currently in the setting where this study was carried out, effective social support systems and comprehensive health insurance schemes are lacking. Thus, parents/caregivers must pay solely for all expenses incurred during the course of the illness out of pocket. This poses a lot of stress on the caregivers. Previous studies indicate that caregiver stress can have a negative impact on the child's psychosocial adjustment and QoL [28, 29]. Therefore, the awareness on the continued need to be on these expensive medications, and experiencing the financial burden on their parents/relatives may have affected their emotional health. In addition, anxiety, worry or fear of progression to ESRD and uncertainty about the eventual disease outcome may also be a contributing factor to poor emotional health. Ruth et al suggested the fear of imminent relapse as the possible reason for the poorer scores in the emotional domain [2]. On the contrary, Selewski *et al* documented that the response or lack of it to steroid therapy had no effect on HRQoL [16]. Eighteen subjects (36%) had the non-MCNS histology type. These patients were also found to be steroid resistant. This is in keeping with reports from several studies that children who are steroid resistant are more likely to have the non-MCNS histology

type [30, 31]. Similar to the finding in those with SRNS, children with the non-MCNS also had poorer emotional and total scores than children with MCNS. Also, these children are the ones that will require the more expensive drugs (calcineurin inhibitors) to achieve remission. Failure to achieve remission and the uncertainty about the possible outcome may account for the lower scores in these domains.

The impact of disease duration on HRQoL in children with NS was found in the physical and emotional domains. While children with less than one year of illness showed worse scores in the physical functioning, those with more than one year had worse emotional scores. This could be explained by the additional finding that children with less than one year of illness constituted the newly diagnosed with shorter period of management. Similar to the finding on the effect of edema, poor scores were noted in item banks two, three, four and eight of the physical domain. The presence of these new symptoms may have affected their daily physical activities. Furthermore, the possibility of not having explored several treatment options due to the inherent relapsing and remitting nature of NS, could account for better emotional scores seen in those with less than twelve months of the disease. In addition, those with longer duration of illness are often faced with challenges of attaining and sustaining remission. Going through numerous steps and processes to achieve this could be emotionally challenging. The alterations in physical appearance (acne, striae, weight gain) from prolonged steroid therapy could affect self-image, self-esteem, peer relationships, and by extension the emotional state. Other researchers have also established the relationship between prolonged steroid use and emotional challenges [32, 33]. Selewski *et al* suggested that pattern of impairment on HRQoL was global but those with longer duration had worse scores in social and school functioning [18]. With longer duration of illness, there is likelihood for the affected children to be away from school. Cumulative school absences therefore, may have affected peer group interaction and academic performance. Non-validation of the PedsQL questionnaire in the indigenous language thereby excluding children who do not understand English language limits this study. Those who were interviewed were literate and can speak and understand English language.

Conclusions

Disease severity evidenced by presence of edema, higher level of proteinuria, steroid resistance, and non-minimal change histology type predispose to lower HRQoL scores. The chronic nature of the disease also showed a negative impact by itself on HRQoL scores. Educators, counselors and psychotherapists should be integrated in the management team. Health care providers should not be complacent with remission only. Information obtained from HRQoL scores should also be addressed.

Ethical Approval

Permission for the use of PedsQL 4.0 was sought and granted by the developer, Dr. James W.Varni at the Mapi Research Trust in France by one of the authors. The ethical approval was obtained from the Human Research and Ethics Committee of the University of Nigeria Teaching Hospital, Enugu, Nigeria prior to the commencement of the study. Information gathered from the participants was treated with utmost confidentiality.

All procedures performed in studies involving human participants were in accordance with ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study. Open Access: This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativeco mmons. org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

Author Contributions

MNR, OOI and OHU envision the study, participated in its design, data collection and coordination of the study and drafted the manuscript. OT, IAN, UAC, IKK, and AAC contributed substantially to data collection, analysis and interpretation and revision of the manuscript. MNR, OOI, OHU, OT, IAN, UAC, IKK, and AAC did the final revision of the manuscript. All authors read and approved the final manuscript for publication.

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