

Medications and Follow-Up Adherence of Children with Nephrotic Syndrome

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Abstract

Background Nephrotic syndrome is one of the most common chronic kidney diseases in children. Its management requires outpatient follow-up and family engagement.

Objective To evaluate the adherence of patients with nephrotic syndrome to the scheduled follow-up visits to the outpatient clinics, and to assess the possible risk factors for non-adherence.

Methods A prospective observational study was carried out on 96 patients with nephrotic syndrome over a period of 1 year. Both regularly scheduled and urgent visits to the outpatient nephrology clinic were recorded. If a patient missed more than 20% of their scheduled clinic appointments throughout the follow-up period, they were considered to be non-adherent.

Results Frequent relapse was the most common presentation encountered in 43.75% of the patients, and the median disease duration was 3.12 years (range 0.25-13.0 years). The study showed that 71 patients (73.96%) had good adherence, while 25 patients (26.04%) were non-adherent. More than half of non-adherent patients (56%) were rural residents. The median disease duration in adherent and non-adherent patients was 3.0 and 4.0 years, respectively, with a significant difference. Furthermore, frequent relapse was more common among non-adherent than adherent patients (64% vs. 36.62%), while steroid-resistant nephrotic syndrome was more common among adherent (21.13%) than non-adherent patients (4%) with a significant difference.

Conclusion Non-adherence was significantly correlated with residency in rural areas and longer disease duration. Frequently-relapsing nephrotic syndrome was more common among non-adherent than adherent patients, while steroid-resistant type was more common among adherents, with a significant difference.

Keywords Nephrotic syndrome, non-adherence, risk factors

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List of abbreviations: AKI = Acute kidney injury, FRNS = Frequently relapsing nephrotic syndrome, NS = Nephrotic syndrome, SRNS = Steroid-resistant nephrotic syndrome, SSNS = Steroid-sensitive nephrotic syndrome

Introduction

Nephrotic syndrome (NS) is one of the most common chronic kidney diseases in children ⁽¹⁾. The incidence is estimated to be 2 to 7 per 100,000 children aged 1 to 18 years worldwide, with a peak age

at diagnosis of 1 to 4 years and a predominance of males ⁽²⁾.

NS is classified into idiopathic, secondary, and congenital depending on the cause and timing of proteinuria ⁽³⁾. Idiopathic NS can be categorized as steroid-sensitive NS (SSNS) and steroid-resistant NS (SRNS) depending on the extent to which the initial standard steroid treatment succeeded ⁽⁴⁾.

Patients who suffer relapses may experience complications such as anasarca, acute kidney injury (AKI), severe infections, or thromboembolic events requiring hospitalization⁽⁵⁾.

As a result, the majority of patients use long-term treatments, such as repeated corticosteroid courses for each relapse of their disease, second-line immunosuppressive medications, including cyclophosphamide, mycophenolate mofetil, and calcineurin inhibitors, may be administered to them to keep their disease in remission⁽⁶⁾.

Outpatient follow-up and family participation are necessary for the management of NS. Because NS necessitates intensive parental home-based monitoring of medicine administration using decreasing doses and an alternate-day ingestion schedule, the complexity of the condition evolves^(7,8).

Treatment failure for chronic illnesses in children may result from non-adherence to prescribed regimens. There were many reasons for not taking the medication as prescribed by the doctor, including forgetting to take it, being away from home, having a busy schedule at school, being worn out from long-term treatment, and drug shortages (delaying their outpatient care visit). Patients with chronic diseases may benefit from self-regulation combined with family education⁽⁷⁾. Non-adherence has been linked in pediatric patients with increased admissions to hospitals, emergency room visits, and higher healthcare costs⁽⁶⁾.

The study aimed to evaluate the adherence of patients with NS to the scheduled follow-up visits to the outpatient clinics and to assess the possible risk factors for non-adherence.

Methods

A prospective observational study was carried out on patients with NS attending the Pediatric Nephrology Consultation Clinic in Al-Imamein Al-Kadimein Medical City and Central Child's Teaching Hospital in Baghdad, Iraq over a period of 1 year, from the 1st of September

2022 to the end of August 2023. During the period of the study, 96 patients were included after obtaining consent from them or their parents. All patients have an age at disease onset >1 and <18 years, and they have idiopathic NS. Children with secondary causes of NS were excluded.

Demographic information was taken, which included age, gender, residency, age at diagnosis of NS, and disease duration. The type of NS was documented according to the number of relapses and response to steroid therapy, the following definitions were applied: Relapse refers to an increase in the first-morning urine protein: creatinine ratio >0.2, urine dipstick protein $\geq 3+$ (300 mg/dL) for 3 consecutive days, or urine protein >40 mg/m²/h. Frequently relapsing NS (FRNS) is defined as two or more relapses during the first six months of terminating the initial therapy or more than two relapses within 12 months. SSNS is achieving remission within 6 weeks of treatment with prednisone at standard dose (60 mg/m²/day or 2 mg/kg/day; maximum 60 mg/day), while SRNS lacks remission despite treatment with daily steroids for 6 weeks⁽⁹⁾.

Inpatient records for the last 3 years were reviewed. The relationship to NS of each hospitalization was assessed. The only hospitalizations included were those that were indicated for the treatment of NS complications. Serious complications, hospitalizations, and length of stay were all recorded. AKI, blood clots, peritonitis, shock, significant edema (anasarca and/or scrotal swelling), or seizures were all considered serious complications⁽⁵⁾. AKI is defined as a rise in serum creatinine by ≥ 0.3 mg/dL from baseline within 48 hours; or ≥ 1.5 times baseline within the previous 7 days, or urine output ≤ 0.5 mL/kg/hr for 6 hours⁽¹⁰⁾.

The review included both regularly scheduled and urgent visits to the outpatient nephrology clinic to treat and monitor NS. Clinic appointments that were completed and missed had been recorded. The number of missed appointments divided by the overall number of

clinic appointments is referred to as the "no-show" percentage. If a patient missed more than 20% of their scheduled clinic appointments throughout the follow-up period, they were considered to be non-adherent ⁽⁵⁾.

The Bioethical Committee of the College of Medicine at the Al-Mustansiriyah University of (No. 11 at July, 2022) approved the study's methods. In order to enroll the patients in the study, informed consents were obtained from them and their parents. The study was concordant with the code of ethics for human studies "Declaration of Helsinki".

Statistical analysis

Statistical package of social sciences (SPSS) software, version 25.0 (SPSS, Chicago), was used to conduct all statistical analyses. A normality test (Shapiro-Wilk test) was applied to continuous data and they were found to be non-normally distributed. Accordingly, they were presented as median and range and analyzed with a non-parametric Mann-Whitney U test. The Chi-square test was used to assess categorical variables, which were presented as numbers and percentages. A statistically significant difference was considered to exist when the p-value was less than 0.05.

Results

Demographic characteristics of patients are shown in table (1). The median age was 8 years (Range 1-15 years) and most cases were males (66.67%). The majority of patients were living in urban areas (65.63%), and the median age of diagnosis was 4 years.

Clinical characteristics of patients are shown in table (2). Frequent relapse was the most common presentation of NS encountered in 43.75% of the patients, followed by infrequent relapse (39.58%) and then steroid resistance (16.67%). The cornerstone of the treatment was steroid which was used alone in 83 patients (86.46%). However, other drugs were used besides steroids in some patients including cyclosporine in 7.29% of the patients, Mycophenolate mofetil in 6.25% and Tacrolimus in 4.17% of them. Patients were infrequently admitted to the hospital with a median of 1.0 admission (range = 0-5 admissions). However, most admitted patients had a relatively prolonged hospital stay with a median of 8.0 days (range 1-50 days). Most admitted patients developed serious complications. Of those, anasarca was the most frequent, presenting in 46.88% of the patients, followed by AKI (15.63%), as shown in table (2). A patient can have more than one serious complication. Other complications included 2 cases of pleural effusion and 7 cases of symptomatic hypertension.

Table 1: Demographic characteristics (n=96)

Variables		Values
Age (years)	Mean±SD	8.0±3.46
	Median	8.0
	Range	1.0-15.0
Gender	Male	64 (66.67%)
	Female	32 (33.33%)
Residency	Urban	63 (65.63%)
	Rural	33 (34.37%)
Age at diagnosis (years)	Mean±SD	4.35±2.73
	Median	4.0
	Range	0.3-12.6

Table 2. Clinical Characteristics of the study population

Variables		Values
Types of NS	Frequently relapsing NS	42 (43.75%)
	Infrequently relapsing NS	38 (39.58%)
	Steroid-resistant NS	16 (16.67%)
Disease duration (years)	Median	3.12
	Range	0.25-13.0
Treatment	Steroid only	83 (86.46%)
	+ cyclosporine	7 (7.29%)
	+ mycophenolate mofetil	6 (6.25%)
	+ tacrolimus	4 (4.17%)
Number of admissions	Mean ± SD	1.41±1.1
	Median	1.0
	Range	0-5
Total hospital stay (days)	Mean ± SD	11.35±9.31
	Median	8.0
	Range	1-50
Serious complications	Anasarca	45 (46.88%)
	Acute kidney injury	15 (15.63%)
	Scrotal oedema	12 (12.5%)
	Peritonitis	8 (8.33%)
	Others	9 (9.37%)

The median total appointments during last 3 years were 20.0 appointments (range 2-133), while the median actual number of visits was 18.0 visits (range 2-105). Thus, the median

number of missed visits was 2.0 (range = 0-28). Taken as a percentage, the median percentage of missed visits was 10% (range 0.0-64.71%) as shown in table (3).

Table 3. Adherence-related parameters

Variables		Values
Total appointment	Median	20.0
	Range	2-133
Number of visits	Median	18.0
	Range	2-105
Missed visits	Median	2.0
	Range	0-28
Percentage of missed visits (%)	Median	10.0
	Range	0.0-64.71

Considering 20% as a cut-off percent for non-adherence, 71 patients (73.96%) had good

adherence, while 25 patients (26.04%) were non-adherent (Figure 1).

More than half of non-adherent patients (56%) were rural residents compared with 26.76% of adherent patients who resided countryside with a significant difference (Table 4).

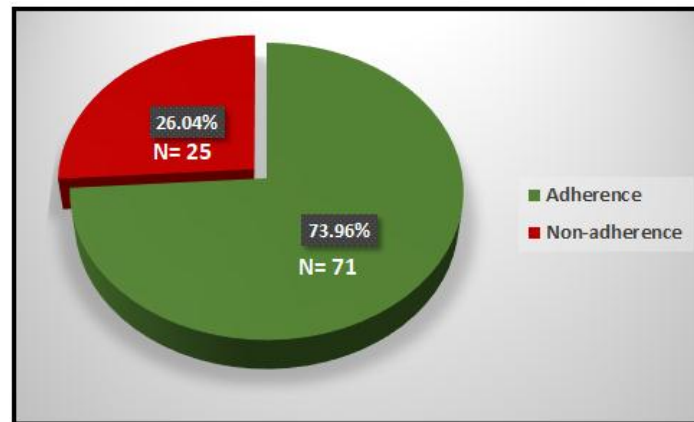


Figure 1. Adherence rate of patients with nephrotic syndrome to regular follow up visits

Table 4. Association between demographic characteristics and adherence

Variables		Adherence (n=71)	Non-Adherence (n=25)	P value
Age (years)	Median	7.5	8.0	0.400
	Range	1.0-15.0	2.0-15.0	
Sex	Male	47 (66.2%)	17 (68%)	0.869
	Female	24 (33.8%)	8 (32%)	
Residency	Urban	52 (73.24%)	11 (44%)	0.008
	Rural	19 (26.76%)	14 (56%)	
Age at diagnosis (years)	Median	4.0	3.6	0.276
	Range	0.33-12.6	1.0-10.0	
Total appointment	Median	21.0	18.0	0.599
	Range	2.0-98.0	8.0-133	

The median disease duration in adherent and non-adherent patients was 3.0 and 4.0 years, respectively, with a significant difference. Furthermore, frequent relapse was more common among non-adherent than adherent patients (64% vs. 36.62%), while SRNS was

more common among adherent (21.13%) than non-adherent patients (4%) with a significant difference. Treatment patterns do differ between the two groups though not significantly (Table 5).

Table 5. Association of clinical characteristics with adherence

Variables		Adherence (n=71)	Non-Adherence (n=25)	P value
Disease duration (years)	Median	3.0	4.0	0.047
	Range	0.25-9.4	1.0-13.0	
Type of NS	Frequently relapsing NS	26 (36.62%)	16 (64%)	0.032
	Infrequently relapsing NS	30 (42.25%)	8 (32%)	
	Steroid-resistant NS	15 (21.13%)	1 (4%)	
Treatment	Steroid only	59 (83.1%)	24 (96%)	0.105
	+ cyclosporine	7 (9.86%)	0 (0%)	0.184
	+ mycophenolate mofetil	6 (8.45%)	0 (0%)	0.334
	+ tacrolimus	3 (4.23%)	1 (4%)	1.00
Number of admissions	Median	1.0	1.0	0.577
	Range	0.0-5	0.0-3.0	
Total hospital stay (days)	Median	6.0	6.0	0.740
	Range	0.0-50	00-36.0	
Serious complications	Anasarca	32 (45.1%)	13 (52%)	0.550
	Acute kidney injury	11 (15.49%)	4 (16%)	0.592
	Scrotal oedema	10 (14.08%)	2 (8%)	0.429
	Peritonitis	6 (8.45%)	2 (8%)	1.0
	Others	7 (9.86%)	2 (8%)	1.0

Discussion

The current study shows that the median age for patients with NS was 8 years (Mean±SD 8.0±3.46 years), which is approximately similar to results found by Samuel et al. (11) and Imbusi et al. (12), while Wang et al. (5), Wang et al. (6) and Setyawati et al. (7) found that the majority of patients with NS were younger than 6 years old (54%, 41%, and 36% respectively), this difference could be explained by the fact that our study was accomplished in tertiary centers, in which patients were referred to them after being diagnosed and started their treatment. Regarding patients' sex, this study demonstrates male predominance, which is supported by Wang et al. (5), Wang et al. (6), Setyawati et al. (7), and Imbusi et al. (12). The majority of study patients reside in urban areas (65.63%), which reflects the geographical locations of the tertiary hospitals in which the study was carried out. A similar result was found by Ali et al. study (13) which was done in the same area. Furthermore, the median age at diagnosis of NS was 4 years (Mean±SD

4.35±2.73), which is supported by Welegerima et al. (14) (5.21±2.66 years), and Hingorani et al. (15).

The most common type of NS in the current study was FRNS, which is found in 43.75%, followed by IRNS (39.58%), while SRNS was the least commonly encountered (16.67%). Approximately similar results were found by Wang et al. (6), Welegerima et al. (14), and Franke et al. (16). The median disease duration was 3.12 years (range 0.25-13.0), and the majority of patients (86.46%) were treated with steroids only, while the minority required 2nd line drugs in addition to the steroids, these results reflect the types of NS in this study in which SRNS was the least common which required immunosuppressive therapy beside steroids. These findings were agreed with Wang et al study (5).

The median number of hospital admissions per year was 1 (range 0-5), with a median length of stay in the hospital was 8 days (range 1-5). This may be attributed to the large number of FRNS in this study, who have mild to moderate

relapses that had been managed at home without hospital admission, and the long duration of hospitalization reflects severe complications that required prolonged treatment inside the hospital. According to research by Wang et al. ⁽⁵⁾, the median hospitalization rate was 0.50 per patient per year, and most patients (71%) experienced at least one hospitalization with an average stay of 4 days. Serious complications developed in 14% of the patients in the first 3 years of follow-up which is lower than the results found in present study.

Regarding complications of NS, 92.7% of patients developed serious complications, in which anasarca was the most commonly encountered (46.88%), followed by AKI and scrotal edema (15.63% and 12.5%, respectively). Kumar et al. study ⁽¹⁷⁾ found that 40.7% of patients developed anasarca, while Franke et al. study ⁽¹⁶⁾ in Germany found that 4.3% developed acute renal failure, which is lower than the result found in the current study. This difference could be attributed to variations in sample size and general characteristics of patients between different countries.

The current study also demonstrated that 73.96% of patients were adherent to the appointed visits to the outpatient clinics for follow-up, while 26.04% were not. Wang et al. study ⁽⁶⁾ which was conducted in USA and Canada found that 36% of patients with newly diagnosed NS were non-adherent with medication on the first survey, while Wang et al. ⁽⁵⁾ study in Atlanta demonstrated that 32% of patients had more than 20% "no-shows" for clinic appointments, and 43% of patients reported poor adherence to NS prescriptions. Non-adherence is very important to be studied because it is a significant factor for treatment failure in chronic diseases in pediatrics ⁽¹⁸⁾.

Non-adherence to clinical follow-up visits was significantly correlated with residency in rural areas in the present study, this could be explained by the remote location of these areas from the city center, in addition to the lower educational levels of these families in comparison to those living in urban areas. In addition, non-adherent patients have

significantly longer disease duration than adherents, which was supported by the Wang et al. study ⁽⁶⁾ and could be explained by the longer duration of illness and suffering may make those patients bored and lose hope from the disease itself, its medications and clinical visits. Furthermore, FRNS was significantly more common among non-adherent patients, while SRNS was more common among adherent ones. Patients with FRNS experienced knowledge about self-medication of recurrent relapses, so they did not seek medical attention and lost their scheduled visits for follow-up, while patients with SRNS had regular visits to the outpatient clinics because of their difficult-to-manage illnesses which required physician look, examination, and decision.

Each age, sex, age of diagnosis, number of hospital admissions, duration of hospitalization, and complications were non-significantly different between adherent and non-adherent patients. Wang et al. study ⁽⁶⁾ found that age was significantly higher in non-adherent patients, this difference with our study could be explained by the different age groups included in that study. The type of medication was non-significantly correlated with adherence to clinical visits in the present study, while the Wang et al. study ⁽⁶⁾ demonstrated a significant association of immunosuppressive medications with non-adherence. This could be explained by the small number of patients who were treated with immunosuppressant medications in our study in comparison with the Wang et al. study ⁽⁶⁾.

Polypharmacy is strongly associated with the possibility of negative outcomes in the use of medications and the increased complexity of pharmacotherapy ⁽¹⁹⁾. Based on the therapeutic regimen's characteristics (such as the number of medications prescribed, dose, and frequency) and the requirement for specific instructions (such as how to crush, break, or dilute pills), pharmacotherapy complexity is in turn identified in several research studies as a contributing factor to non-adherence to treatment, hospitalization, and re-hospitalization. These problems are frequently seen in pediatrics due to the lack of

pharmaceutical preparation for that population, which necessitates fractioning or diluting of pills and capsules to individualize doses, which results in increasing pharmacological complexity^(20,21).

In conclusion, non-adherence to scheduled visits to the outpatient clinics was encountered in 26.04% of patients with NS. Non-adherence was significantly correlated with residency in rural areas and longer disease duration. Furthermore, FRNS was more common among non-adherent than adherent patients, while SRNS was more common among adherent than non-adherent patients with a significant difference.

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Author contribution

Dr. Hussein contributed to study design and research supervision. Dr. Ali contributed to data analysis, draft manuscript preparation, and the critical revision of the paper. Both authors contributed to supervision, funding, and the final approval of the version to be published.

Conflict of interest

The authors have no conflict of interest.

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