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Frequency of Relapse in Nephrotic Syndrome Children Treated with Prednisolone

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Abstract

Background: Relapsing-remitting idiopathic nephrotic syndrome is a childhood disorder that presents with a 20-30% lifetime occurrence rate of a single episode, while the remaining individuals experience relapses.

Objective: Investigate the correlation between demographic and biochemical factors and the occurrence of relapses in children who are responsive to prednisolone.

Patients and Methods: A cross-sectional analysis was conducted at the Kerbala Teaching Hospital for Children in Iraq, spanning from August 1st to November 2023. There was a correlation between relapse and factors such as gender, age, albumin serum level, total cholesterol level and proteinuria.

Results: Out of the 80 children diagnosed with steroid-sensitive nephrotic syndrome, 15 (18.8%) didn't experience any relapses, 44 (55%) had infrequent relapses and 21 (26.2%) had frequent relapses. The patients' ages ranged from one to sixteen years. The male population accounted for 54% of the total, and the female population accounted for 26%. There were no significant differences in age, gender and blood cholesterol levels between the different groups (p values 0.224, 0.488 & 0.319, respectively). A strong positive relationship was found between low levels of serum albumin, proteinuria and recurring relapses (with p-values of 0.016 and 0.042, respectively).

Conclusion: There was a significant correlation between relapses and reduced levels of serum albumin and proteinuria.

تكرار الانتكاس في الأطفال الذين يعانون من متلازمة التناذر الكلوي المعالجين بالبريدنيزولون

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الخلاصة

المقدمة

متلازمة التناذر الكلوي المتكررة والمستمرة مجهولة السبب هي اضطراب يحدث في مرحلة الطفولة ويتميز بحدوث نوبة واحدة بنسبة 20-30% طوال العمر، بينما يعاني الأفراد الآخرون من انتكاسات متكررة.

الهدف

دراسة العلاقة بين العوامل الديموغرافية والكيميائية الحيوية و حدوث الانتكاسات لدى الأطفال الذين يستجيبون للبريدنيزولون.

المرضى وطرق العمل

أجريت هذه الدراسة المقطعية في مستشفى كربلاء التعليمي للأطفال في العراق، من 1 أغسطس إلى نوفمبر 2023. تم العثور على علاقة بين الانتكاسات وعوامل مثل الجنس، العمر، مستوى الألبومين في المصل، مستوى الكوليسترول الكلي والبيلة البروتينية.

النتائج

من بين 80 طفلًا تم تشخيصهم بمتلازمة التناذر الكلوي المستجيبة للأدوية الستيرويدية ، لم يعاني 15 (18.8%) من أي انتكاسات، وكان 44 (55%) يعانون من انتكاسات غير متكررة، في حين كان 21 (26.2%) يعانون من انتكاسات متكررة. تراوحت أعمار المرضى من سنة إلى 16 سنة. شكل الذكور 54% من إجمالي الحالات، بينما شكلت الإناث 26%. لم تكن هناك اختلافات ذات دلالة إحصائية في العمر والجنس ومستويات الكوليسترول في الدم بين المجموعات المختلفة (القيم الاحتمالية 0.224، 0.488 و 0.319 على التوالي).
وجدت علاقة إيجابية قوية بين انخفاض مستويات الألبومين في المصل والبيلة البروتينية والانتكاسات المتكررة .)بقيم احتمالية 0.016 و 0.042 على التوالي (

الاستنتاج

كانت هناك علاقة ذات دلالة إحصائية بين الانتكاسات وانخفاض مستويات الألبومين في المصل والبيلة البروتينية .

1. Introduction

Nephrotic syndrome is a prevalent kidney disease among children, distinguished by the presence of heavy proteinuria (>40 mg/m^2/hr; 1 g/m^2 daily) and hypoalbuminemia (serum albumin <3 g/dL). It is Characterized by edema and heavy proteinuria (Sinha et al., 2021). The annual incidence and prevalence of nephrotic syndrome are two to seven new cases and sixteen new cases per one hundred thousand children, respectively. The incidence of nephrotic syndrome in the adult population is three new cases per one hundred thousand adults annually (Politano et al., 2020). Nephrotic syndrome is predominantly idiopathic, with minimal change disease accounting for approximately 80-90% of these cases, steroid therapy is effective in approximately 80% of cases involving minimal change disease; however, 70–85% of these patients will experience a relapse, and 50% will develop relapses that occur Frequently, the most prevalent age at presentation is 2 years, although the age range afflicted is typically 1 to 10 years (Hodgin et al., 2022). Approximately 80-90% of children who are prescribed Steroid-Sensitive Nephrotic Syndrome (SSNS) undergo one or more subsequent relapses, which may manifest as frequent or infrequent relapses or steroid dependence (Ali et al., 2022). The International Study for Kidney Disease in Children (ISKDC) initially estimated a relapse rate of 60%. A small percentage of individuals (approximately 15%) are dependent on steroids, whereas 25%–40% of those who respond to prednisolone experience infrequent relapses. When it comes to relapses, relapse therapy has conventionally included using prednisone daily until remission, followed by alternating days for the next four weeks; treatment is then discontinued or tapered over the course of four to eight weeks (Shanta et al., 2023). Relapse is associated with a considerable number of complications, elicits anxiety in patients, and places a considerable financial burden. Furthermore, the prognosis for the progression of the disease becomes challenging once the initial recurrence has been treated (Akter et al., 2020). To study the potential correlated factors that contribute to the increased incidence of relapse in children with nephrotic syndrome and the relative frequency of relapse in this patient population.

2. Patients and Methods

This observational cross-sectional study was conducted at Kerbala Teaching Hospital for Children from August to November 2023. After approval by the scientific and ethical committee of College of Pharmacy, University of Kerbala. Informed consent was taken from each participant (or relative) before starting the study. A total of 80 patients, spanning in age from 1 to 16 years, were included in this study and were found to have cases of SSNS. Patients with congenitally acquired NS, incomplete data, steroid-resistant NS, or ages below 1 or exceeding 16 years were excluded from the study. Based on the following criteria, NS was diagnosed: Albustix >2+ (for older children with collected 24-hour urine or non-toilet-trained children), heavy proteinuria exceeding 40 mg/h/m^2 (for non-toilet-trained children or complex collections of 24-hour urine), hypoalbuminemia below 2.5 g/dL or edema, and hyperlipidemia with total cholesterol ranging from 170 to 200 mg/d. The protocol established by the International Society for Kidney Disease in Children (ISKDC) guided the clinical approach at the pediatric nephrology unit. Following the initial four weeks of Prednisone treatment at a rate of 60 mg/m^2 divided daily, the dosage was decreased to 40 mg/m^2 divided daily to accommodate the duration of the attack. After this, four weeks of alternate-day therapy were administered prior to its tapering. Relapse was controlled with prednisone administered at a dose of 40 mg/m^2

on alternate days for a duration of four weeks. Following the collection of urine, prednisone was administered at a daily dose of 60 mg/m^2 for three days (Shanta et al., 2023, Ali et al., 2016). The definitions that followed were incorporated: Relapsed is defined as the presence of proteinuria over 40 mg/h/m^2 or 50 mg/kg/day, or a positive result on Albustix >2+ for three consecutive days following a period of remission. Frequent relapse was defined as the occurrence of 2 or more relapses within 6 months of the initial response, or 4 or more relapses within a period of 1 year. Infrequent relapse was defined as the occurrence of 1 recurrence within 6 months, or 1-3 relapses within 12 months. Remission is characterized by proteinuria levels below 4 mg/h/m^2 or the absence of protein on a protein stick test for 3 consecutive days. Steroid therapy can lead to complete remission, known as SSNS. Steroid-resistant nephrotic syndrome (SRNS) refers to patients who do not achieve remission after an 8-week treatment with corticosteroids (Niaudet and Boyer, 2009, Shaker et al.)

2.1. Data Collection

At the time of enrollment, the participants' demographic and clinical information was collected on a pre-established document. Age, gender, proteinuria (as detected by a urine dipstick in the wee hours of the morning), S. albumin, and S. cholesterol and relapse incidence were recorder. Following routine blood testing, blood samples were collected in the blood collection area of the hematology laboratory.

2.2. Statistical Analysis

Software Package for the Social Sciences (SPSS 26) will be utilized to conduct the statistical analysis. The numerical data were descriptively represented by the mean and standard deviation of the mean (Mean ± STD), whereas the non-numerical data were presented in the form of percentages and numbers. The assessment of data normality was performed utilizing the Shapiro–Wilk test. Age and other numerical data that follow a normal distribution will be analyzed using the independent sample T-test and the one-way ANOVA-post-hoc LSD test, respectively. Albumin, cholesterol, and protein urea, which have non-normal distributions numerically, will be analyzed utilizing nonparametric tests and legacy dialogs, specifically the Kruskal Wallis test. The Chi-square test will be employed to analyze the non-numerical data. P values that are smaller than 0.05 will be deemed to be statistically significant.

3. Results

This study involved 80 children who had been diagnosed with SSNS. We identified three subgroups of SSNS based on age, gender, and biochemical findings: NO relapse, FR (frequent relapse) and IFR (infrequent relapse). The relapse rate for childhood INS is detailed in Table1. 15 patients (18.8%) did not experience a relapse, while 44 (55%) had IFR and 21 patients (26.2%) had FR.

Table1: Distribution of Patients According to Frequency of Relapse

		N	Percentage
Relapse	**NO**	15	18.8%
	Infrequent	44	55.0%
	Frequent	21	26.2%
Total		80	100.0%

The following data was obtained from the demographic data of the study group: Children ranged in age from one to sixteen years at the time of the study. In terms of gender-based distribution of NS, it was observed that males constituted the plurality, comprising 54 of the total patients, whereas females constituted 26.

As shown in Table2, age differences between groups weren't statistically significant (p=0.224). Regarding gender, no statistically significant distinction was found between groups (p=0.488). Male participants comprised 11 (73.3%) in the no relapse group, 31 (70.5%) in the IFR group, and 12 (57.1%) in the FR group; females accounted for 4 (26.7%), 13 (29.5%), and 9 (42.9%), respectively.

Table2: Demographic Data of Children with Nephrotic Syndrome

Variables		**Relapse of nephrotic syndrome**			***P* – value**
		No (n=15)	**Infrequent (n=44)**	**Frequent (n=21)**	
Age (y)		7.07 ± 4.85	8.66 ± 3.22	9.1 ± 3.28	0.224
Gender	**Male**	11 (73.3%)	31 (70.5%)	12 (57.1%)	0.488
	Female	4 (26.7%)	13 (29.5%)	9 (42.9%)	
Data Present as Mean ± SD and No (%)					

As shown in Table3, there were statistically significant variations between groups in serum albumin (g/ml) and proteinuria (mg/ml) (p=0.016 and p=0.042, respectively). There was no significant correlation observed between relapse and level of cholesterol (mg/mL) (p=0.319). Fig.1 and Fig.2 presents data showing significant diminishment of serum albumin levels in all categories of relapse: frequent (mean = 2.85 ± 1.25), infrequent (mean = 3.35 ± 1.09), and no (mean = 3.99 ± 0.97). In contrast, Fig.3 indicate that proteinuria is greatest in the category of frequent relapse (244.76 ± 340.07), followed by infrequent relapse (107.73 ± 259.02), and finally, no relapse (23 ± 78.66).

Table 3: Correlation Between Biochemical Findings and Relapses in Patients with Nephrotic Syndrome

Variables	**Relapse of Nephrotic Syndrome**			***P* -value**
	No (n=15)	**Infrequent (n=44)**	**Frequent (n=21)**	
S.albumin (g/ml)	3.99 ± 0.97	3.35 ± 1.09	2.85 ± 1.25*	0.016
S.cholesterol (mg/ml)	243.71 ± 133.68	233.01 ± 128.69	276.53 ± 129.75	0.319
Proteinuria (mg/ml)	23 ± 78.66	107.73 ± 259.02	244.76 ± 340.07$^{*\#}$	0.042
(Data present as mean ± STD), Significant effect (P < 0.05) compared to no relapse group, Significant effect (P < 0.05) compared to infrequent group.				

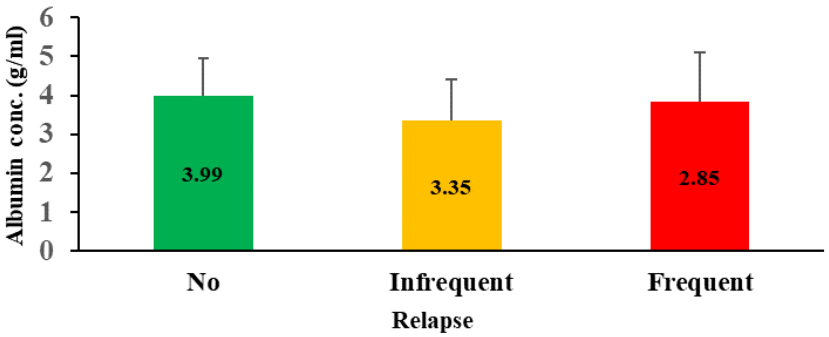

Figure1: Comparison of Serum Albumin Concentration Across Relapse Frequencies

The bar chart illustrates the mean serum albumin concentration (g/ml) among three patient groups based on relapse frequency: **No relapse** (green): 3.99 g/ml, **Infrequent relapse** (yellow): 3.35 g/ml, **Frequent relapse** (red): 2.85 g/ml. A decreasing trend in albumin levels is observed with increasing relapse frequency. Error bars represent the standard deviation.

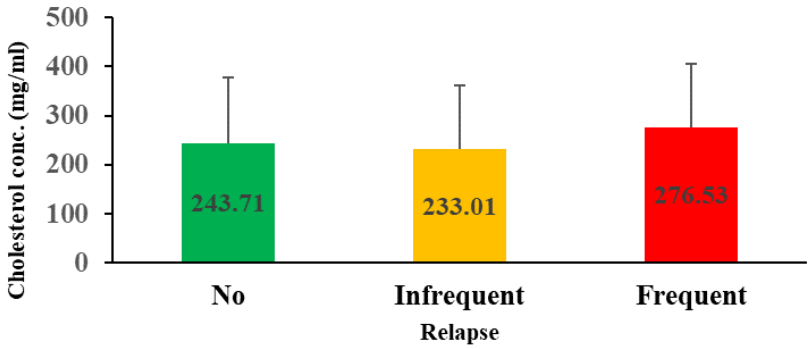

Figure2: Comparison of Serum Cholesterol Concentration Across Relapse Frequencies

The bar chart shows the mean serum cholesterol levels (mg/ml) in patients grouped by relapse frequency: **No relapse** (green): 243.71 mg/ml, **Infrequent relapse** (yellow): 233.01 mg/ml, **Frequent relapse** (red): 276.53 mg/ml. An increase in cholesterol concentration is observed in the **frequent relapse** group compared to the other groups. Error bars represent the standard deviation.

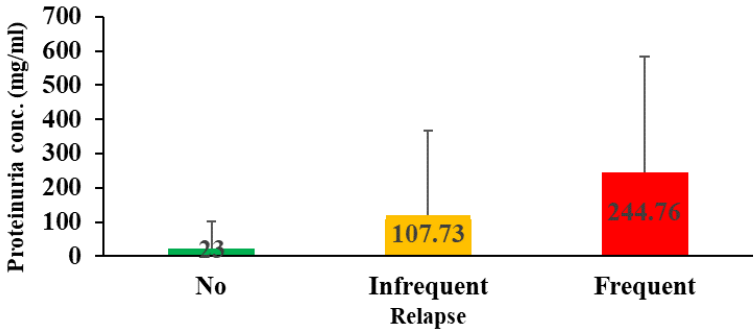

Figure3: Comparison of Proteinuria Concentration Across Relapse Frequencies

The bar chart displays the mean proteinuria concentration (mg/ml) among patients categorized by relapse frequency: **No relapse** (green): 23 mg/ml, **Infrequent relapse** (yellow): 107.73 mg/ml, **Frequent relapse** (red): 244.76 mg/ml. A marked increase in proteinuria levels is observed with increasing relapse frequency. Error bars indicate standard deviation.

4. Discussion

Nephrotic syndrome is a recurring and chronic kidney illness that has a higher occurrence rate compared to other kidney disorders. The very varied incidence of relapses is linked to several risk factors. Male patients predominated over female patients, a finding consistent with previous research (Ali et al., 2022, Ali et al., 2016, Shaker et al., Noer, 2005).(Rahi et al., 2009) found no statistically significant correlation between gender and relapse frequency, similar to the findings of the present study. The statistical insignificance of the variation in FR and IFR by gender indicates that sex is an inadequate predictor variable. The present findings diverge from those of prior research conducted by (Akter et al., 2020, Hiraoka et al., 1995). FR is negatively correlated with gender, according to a number of investigations (Constantinescu et al., 2000, Fujinaga et al., 2011, Sinha et al., 2012). (Andersen et al., 2010) found that male gender remained associated with an increased risk of steroid dependence and FR, irrespective of the length of the steroid course. In another study, male gender was identified as a predictor of FR (Noer, 2005). Consistent with prior investigations carried out by (Ali et al., 2016, Constantinescu et al., 2000, Fujinaga et al., 2011, Takeda et al., 2001), our results do not suggest any correlation between age at presentation and subsequent relapses among patients diagnosed with NS. On the contrary,(Andersen et al., 2010, Sarker et al., 2012) reported a remarkable correlation between age at presentation and the subsequent rise in the frequency of relapses. According to an Indian study, individuals diagnosed with FR exhibited a younger age at disease onset, and the incidence of relapses decreased as age increased (Sinha et al., 2012). The observed inconsistency could be attributed to variations in idiopathic NS patterns among different ethnic groups and racial disparities in the study populations of different research studies (Andersen et al., 2010). Following this, 15 patients (18.8%) did not experience a relapse, 44 patients (55%) had fewer than two relapses (IFRNS), and 21 patients (26.2%) had more than two relapses (FRNS). This observation differs significantly from the results reported by (Shanta et al., 2023, Chwat et al., 2014), in which the most prevalent subgroup was frequently relapsing nephrotic syndrome. Conversely, numerous other researchers, including (Karim, 1999) and (Gulati et al., 1997), documented infrequently relapsing nephrotic syndrome as the most prevalent subgroup. The biochemical results indicated a statistically significant correlation between low serum albumin levels and frequent relapses. The outcome bears resemblance to Prior research that has documented a correlation between relapse and deficient serum albumin levels ($\leq$ 15 g/l) (Shanta et al., 2023, Takeda et al., 1996). The levels of serum albumin and proteinuria showed significant differences between the FR and IFR groups ($p=0.016$ & $p=0.042$, respectively), while there was no significant difference in serum cholesterol levels ($p=0.319$). Our research findings demonstrate that a decreased blood albumin level is really a significant risk factor for recurrent relapse of nephrotic syndrome.

5. Conclusion

This study indicates that infrequent relapse was recorded more frequently than frequent relapse in children with steroid sensitive nephrotic syndrome with an abundance of males. A notable correlation was observed between the frequency of relapse and hypoalbuminemia and proteinuria ($p=0.016$ and $p=0.042$). These results will facilitate the timely detection of infants with frequent relapse allowing for appropriate treatment.

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