ORIGINAL RESEARCH

To assess the risk variables associated with recurrence in pediatric nephrotic syndrome

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Received date: 25 February, 2024 Acceptance date: 29 March, 2024

ABSTRACT

Background: Nephrotic syndrome (NS) is the predominant renal disorder in children and is distinguished by edema, extensive proteinuria, low levels of albumin, and elevated lipid levels. The therapy of this disease continues to face a significant challenge due to a high recurrence rate. **Aim:** To assess the risk variables associated with recurrence in pediatric nephrotic syndrome. Material and methods: We examined 100 children admitted to the hospital with NS. Patients who met the ISKDC criteria for the diagnosis of NS, which includes having excessive protein in the urine (proteinuria >40 mg/m2/hour or 50mg/kg/day; urinary protein/creatinine ratio >2.0; or dipstick ≥ 2+), low levels of albumin in the blood (serum albumin < 2.5 g/dL), swelling, and high levels of cholesterol in the blood (serum cholesterol >200 mg/dL), were subjected to further analysis. Relapse was defined as the presence of urine protein at a level of 2+ or higher (or proteinuria above 40 mg/m2/hour) for three days within a week. **Results:** The average age was 9.15±1.76 years. It was observed that 55% of the patients had a normal nutritional condition, 75% had normal blood pressure, and 64% showed no signs of infection at the time of diagnosis. The laboratory findings indicated that most patients (90%) had normal creatinine levels, whereas over half (52%) showed hematuria. The chi-square test indicated that there was no statistically significant disparity in terms of gender or age between the two groups. No statistically significant differences were seen between the relapsed and non-relapsed groups in terms of hypertension, infection, serum creatinine level, or hematuria. Nevertheless, a notable disparity in the nutritional condition of the participants was identified between the relapsed and non-relapsed groups, with a statistically significant difference (P=0.01). **Conclusion:** Ultimately, the nutritional condition of children at the moment of diagnosis might serve as a risk factor for the recurrence of juvenile nephrotic syndrome. If the patient with NS is malnourished, clinicians should provide nutritional treatment and reassess the patient's condition at least six months after receiving steroid medication.

Keywords: Recurrence, Pediatric, Nephrotic syndrome

INTRODUCTION

Nephrotic syndrome is the clinical presentation of glomerular disorders linked to a significant amount of protein in the urine, known as nephrotic range proteinuria. Nephrotic range proteinuria is characterized by proteinuria over 3.5 grams in a 24-hour urine collection or a protein-to-creatinine ratio of more than 2. The three clinical manifestations often seen in nephrotic syndrome resulting from excessive urine protein loss are hypoalbuminemia (≤2.5g/dL), edema, and hyperlipidemia (cholesterol >200mg/dL). 1 Nephrotic syndrome is a prevalent and significant illness in pediatrics, even in healthy children. Roughly half of the children that are afflicted fall between the age range of 1 year and six months to 5 years. Even the mildest type of nephrotic syndrome is inherently a recurring condition, meaning that any new instance is expected to experience symptoms of the illness for a certain period.2

The majority of children (90%) diagnosed with nephrotic syndrome suffer from a kind of idiopathic nephrotic syndrome (INS). The most common form (85%) of idiopathic nephrotic syndrome is minimal change nephrotic syndrome (MCNS), and over 95% of cases of minimal change nephrotic syndrome show a positive response to steroid treatment.3 However, idiopathic nephrotic syndrome is a persistent condition characterized by recurring episodes. Infection is a significant factor that leads to recurrence in minimal change nephrotic syndrome. Preventing and treating infections might help decrease proteinuria without the need for steroids.4 A relapse is typically

triggered by an upper respiratory tract infection (URTI) or a fever episode, and sometimes there is no clear explanation.5 Asymptomatic urinary tract infection may be a significant and often overlooked factor contributing to recurrence.[6]

The frequency of relapses exhibits significant variability. Within one year, some individuals have less than three relapses, while others experience more than four relapses. A global investigation of kidney illness in children first documented a recurrence rate of 60%. However, further evidence indicates that the relapse rate may range from 76% to 90%, with an exceptionally high risk of relapse, up to 50%, in cases that regularly recur.7

Being young and having a low blood protein level at the beginning are separate factors that increase the chance of recurrence.7 Experiencing a relapse during the first year is a strong and separate indicator of future relapses. Additionally, relapsing within the first six months after the first presentation strongly indicates the progression of the following condition. In our nation, the significant challenges in the early identification and treatment of relapse include poverty, insufficient healthcare infrastructure, a poorly structured referral system, and a need for more need for sufficient understanding among parents about the progression of diseases. Therefore, accurately forecasting and averting risk factors is crucial for effectively managing pediatric nephrotic syndrome.

MATERIAL AND METHODS

The research was carried out at the Department of Pediatrics. During the research period, we examined a total of 100 children who were admitted to the hospital with INS. Patients who met the ISKDC criteria for the diagnosis of NS, which includes having excessive protein in the urine (proteinuria >40 mg/m2/hour or 50mg/kg/day; urinary protein/creatinine ratio >2.0; or dipstick ≥ 2+), low levels of albumin in the blood (serum albumin < 2.5 g/dL), swelling, and high levels of cholesterol in the blood (serum cholesterol >200 mg/dL), were subjected to further analysis. Relapse was defined as the presence of urine protein at a level of 2+ or higher (or proteinuria above 40 mg/m2/hour) for three days within a week. This definition applies to patients who had previously remission during the first six months of steroid treatment. Non-relapse was defined as the absence of proteinuria, shown by a negative (-) or trace (±) result, or proteinuria below 4 mg/m2/hour for three consecutive days in a week within six months after receiving steroid medication.

Nutritional status refers to an individual's nutrition condition, as determined by the ratio of body weight to body height. This ratio is measured according to the CDC-NCHS 2000 standard for children older than five years and the WHO standard for children aged five years or younger. Hypertension is characterized by having systolic and diastolic blood pressure that exceeds 95th percentile, depending on age and gender, consistently measured over three consecutive occasions. The normal range for creatinine is 0.3-1.2 mg/dL, whereas any amount of creatinine over 1.2 mg/dL is considered elevated. The patients had several infections upon admission, in addition to the relapsed NS that was diagnosed and documented in their medical records. These infections included pneumonia, dermatological infection, and urinary tract infection. Dropouts are those who fail to attend the subsequent checkpoint. The participants were categorized into two groups: group A consisted of children with INS who experienced a relapse after receiving steroid therapy for a maximum of 6 months, while group B consisted of children with INS who remained in a state of remission for at least the initial six months after receiving steroid therapy. The research excluded patients with systemic and chronic disorders, congenital nephrotic syndrome, steroid resistance, and inadequate medical records (including demographic and laboratory data). The variables that were measured for all subjects included age, sex, height, body weight, history of infection, blood pressure, and laboratory results such as serum protein, serum albumin, serum cholesterol, serum creatinine, complete blood count, and urinalysis, at the time of the NS diagnosis. The data were analyzed using univariate analysis on a categorical scale, with frequency and corresponding percentages reported. The differences between groups were assessed using a Chi-square test, a kind of bivariate analysis. The statistical program SPSS was used for these analyses. Variables with a P value of less than 0.05 in bivariate analysis were deemed significant and were subjected to multivariate analysis.

RESULTS

This research includes a cohort of 100 children diagnosed with INS. Of all the patients, 67% were aged five years or older, ranging from 2 to 17 years. The average age was 9.15±1.76 years. The population consisted of 65% boys and 35% girls, resulting in a male-to-female ratio of 1.86:1. Out of the total number of participants, 60% were classified as belonging to the relapsed group, whereas 40% were classified as belonging to the non-relapsed group. It was observed that 55% of the patients had a normal nutritional condition, 75% had normal blood pressure, and 64% showed no signs of infection at the time of diagnosis. The laboratory findings indicated that most patients (90%) had normal creatinine levels, whereas over half (52%) showed hematuria. The attributes of the subjects are shown in Table 1. A comparative analysis was conducted to assess the potential risk factors for relapse in both groups. The chi-square test indicated that there was no statistically significant disparity in terms of gender or age between the two groups. No statistically significant differences between the relapsed and non-relapsed groups regarding hypertension, infection, serum creatinine level, or hematuria were seen. Nevertheless, a notable

disparity in the nutritional condition of the participants was identified between the relapsed and non-relapsed groups, with a statistically significant difference (P=0.01). The relapsed group had significantly higher proportions of undernourished and poorly nourished patients compared to the non-relapsed group (Table 2).

Table 1: Basic parameter of the participants

	Number	Percentage
Gender		
Male	65	65
Female	35	35
Age at diagnosis		
Below 5 years	67	67
Above 5 years	33	33
Nutritional status		
Normal	55	55
Undernourished	35	35
Poorly nourished	10	10
Hypertension		
Yes	25	25
No	75	75
Creatinine level		
Normal	90	90
Increased	10	10
Hematuria		
Yes	52	52
No	48	48
Infection at diagnosis		
Yes	36	36
No	64	64
Diagnosis		
Relapsed	60	60
Non-relapsed	40	40

Table 2: Comparison of possible risk factors for relapse between the relapsed and non-relapsed groups

	Number	Relapse=60	Non-relapsed=40	P value
Gender				0.28
Male	65	42	23	
Female	35	18	17	
Age at diagnosis				0.22
Below 5 years	67	40	27	
Above 5 years	33	20	13	
Nutritional status				0.01
Normal	55	29	26	
Undernourished	35	25	10	
Poorly nourished	10	6	4	
Hypertension				0.12
Yes	25	15	10	
No	75	45	30	
Creatinine level				0.17
Normal	90	55	35	
Increased	10	5	5	
Hematuria				0.15
Yes	52	38	14	
No	48	22	26	
Infection at diagnosis				0.18
Yes	36	20	16	
No	64	40	24	

DISCUSSION

Nephrotic syndrome is a kidney illness that has a more significant occurrence rate in comparison to other kidney disorders. The majority of children with nephrotic syndrome suffer from a kind of idiopathic nephrotic syndrome.[10] This is a persistent condition that tends to recur.11 The frequency of relapses may vary significantly across individuals, with some experiencing ≤3 Relapses per year (considered rare) and others having ≥ four relapses per year (considered frequent).[10] Various risk variables are linked to the frequency of relapses. A comprehensive study was conducted on a total of 100 instances of recurrent nephrotic syndrome.

In our research, the recurrence rate in idiopathic NS was 60%, with a ratio of 1.86 boys to every female. The ratio we observed, 1.8:1.12, was comparable to the ratio described by Constantinescu et al. Our relapse incidence was lower than the 59.3% reported by Mishra et al.13 in India. In our research, we categorized the age of patients at the time of diagnosis into two groups: those who were five years of age or less and those who were older than five years of age.

The findings were consistent with the research conducted by Ali SH et al., which found that the age range of 1-5 years was the most prevalent, accounting for 51 patients (63.7%) out of a total of 80 cases.14 A research conducted by Sarker MN et al. discovered that within a sample of 100 patients, the majority (67%) fell between the age range of 2-6 years, with an average age of 5.3±2.1 years.15 The research conducted by Andersen RF et al. also observed a prevalence of individuals under the age of 6.16

Bivariate analysis showed that there was no statistically significant difference in the age at the time of diagnosis between the relapsed and non-relapsed groups (P<0.22), which is consistent with research conducted by Ali et al. (P=0.708).14Although the exact mechanism of INS is not yet understood, it has been suggested that INS may result from compromised T-cell activity and the existence of aberrant T-cell clones that produce glomerulotoxic lymphokines, which are chemical messengers circulating in the body. These mediators enhance the glomerular basement membrane's permeability, leading to proteins in the urine (proteinuria). There is a suspicion that abnormal T-cells are being replicated in the thymus, which is most active throughout childhood.

The current investigation could not find any significant correlation between hypertension and relapse status. Research conducted by Noer MS et al. revealed no significant correlation between hypertension and relapses (p value= 0.340).[9] The lack of a meaningful correlation in this research may be due to the limited number of hypertension individuals. Our observation revealed that the only statistically significant difference between the relapsed and non-relapsed groups was regarding nutritional status (P=0.01), where a more substantial proportion of inadequately fed individuals had relapsed. However, Noer et al. discovered that the nutritional state of their patients did not have a significant impact, as shown by statistical analysis. There were no significant variations in serum creatinine or hematuria levels between the relapsed and non-relapsed groups, as demonstrated by P-values of 0.17 and 0.15, respectively. Nevertheless, Sarker et al. discovered that reduced levels of protein and serum albumin are associated with an increased risk of recurrent relapse.[15]

CONCLUSION

Ultimately, the nutritional condition of children at the moment of diagnosis might serve as a risk factor for the recurrence of juvenile nephrotic syndrome. If the patient with NS is malnourished, clinicians should provide nutritional treatment and reassess the patient's condition at least six months after receiving steroid medication. We recommend doing more research on pediatric nephrotic syndrome without imposing a six-month time constraint. These studies should further evaluate potential risk factors for recurrence. In minimal change nephrotic syndrome preventing and treating infections might help decrease proteinuria without the need for steroids.[4] A relapse is typically triggered by an upper respiratory tract infection (URTI) or a fever episode, and sometimes there is no clear explanation.[5] Asymptomatic urinary tract infection may be a significant and often overlooked factor contributing to recurrence.[6]The frequency of relapses exhibits significant variability. Within one year, some individuals have less than three relapses, while others experience more than four relapses. A global investigation of kidney illness in children first documented a recurrence rate of 60%. However, further evidence indicates that the relapse rate may range from 76% to 90%, with an exceptionally high risk of relapse, up to 50%, in cases that regularly recur.[7]Being young and having a low blood protein level at the beginning are separate factors that increase the chance of recurrence.[7] Experiencing a relapse during the first year is a strong and separate indicator of future relapses. Additionally, relapsing within the first six months after the first presentation strongly indicates the progression of the following condition. In our nation, the significant challenges in the early identification and treatment of relapse include poverty, insufficient healthcare infrastructure, a poorly structured referral system, and a need for more need for sufficient understanding among parents about the progression of diseases. Therefore, accurately forecasting and averting risk factors is crucial for effectively managing pediatric nephrotic syndrome.

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