Risk Factors for Idiopathic Nephrotic Syndrome Relapse in Pediatric Age

Brief report

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ABSTRACT

Introduction. Eighty percent of children with primitive nephrotic syndrome (NS) will have at least one relapse in their life. Specific risk factors could be associated with a higher incidence of relapses and a worse prognosis. This study aims to deepen the demographic and onset-related risk factors in children with known diagnosis of primitive NS attending the Pediatric Nephrology Unit of the University Hospital of Padua.

Methods. Observational, descriptive study of all children (1-11 years old) with a known diagnosis of Primitive NS who attended our Pediatric Nephrology Unit between 1 January 2002 and 31 March 2023.

Results. 49 patients were involved. 79.5% had at least one episode of NS relapse during their lifetime. 69.4% were classified as frequently relapsing or steroid-dependent NS. The relapse risk factor “non-Western ethnicity” was related to a worse prognosis and steroid-dependent NS classification ($p = 0.041$). The onset-related risk factor “thrombocytosis” appears to be related to a better prognosis ($p = 0.03$).

Conclusion. The relapse risk factors “non-Western ethnicity” and “thrombocytosis” are characterized by worse and better prognosis, respectively. This evidence could support the follow-up of primitive NS in pediatric age.

KEYWORDS: nephrotic syndrome relapse, risk factors, ethnicity, thrombocytosis

Introduction

Eighty percent of children with primitive nephrotic syndrome (NS) will have at least one relapse in their life. Among these, fifty percent will be affected by frequently relapsing or steroid-dependent NS [1]. It is very difficult to predict NS relapses. At the same time, it is historically known that fifty percent of treated patients are affected by relapses in the first 6 months [2]. Moreover, it is demonstrated that more relapses are associated with a worse prognosis [1]. Several studies demonstrated that specific risk factors for NS relapses could be associated with a higher incidence of NS relapses. On the one hand, demographic risk factors, such as male sex, atopy, rural background, low socioeconomic status, and non-Western ethnicity, are involved. On the other hand, onset NS-related risk factors are associated with more relapses, such as age < 5 years, reduced serum albumin and serum total protein, reduced nutritional status, remission no sooner than two weeks of steroid therapy, concurrent infectious episode, poor compliance in steroid therapy [4, 8]. This study aims to deepen the demographic and onset-related risk factors for NS relapse in children with known diagnosis of primitive NS attending the Pediatric Nephrology Unit of the University Hospital of Padua.

Methods

We performed an observational, descriptive study of all children (1-11 years old) with a known diagnosis of Primitive NS who attended our tertiary Pediatric Nephrology Unit between 1 January 2002 and 31 March 2023. Starting from their nephrological history, they were classified into the categories “frequently relapsing” (FR), “steroid-dependent” (SD), and “non-frequently relapsing non-steroid-dependent” (NFRNSD). Specifically, FR NS was defined by the presence of > 2 relapses in 6 months or > 3 relapses in 12 months; SD NS was determined by 2 or more relapses during steroid therapy layover or onset of relapse within 15 days after its discontinuation; finally, NFRNSD NS was described by the presence of < 2 relapses in 6 months or < 3 relapses in 12 months and the absence of dependence on steroid therapy. Moreover, the presence of specific risk factors for primitive SN relapses was assessed. Specifically, demographic risk factors were represented by male sex and non-Western ethnicity. Onset-related risk factors were represented by age <5 years, reduced serum albumin and serum total protein levels, reduced nutritional status, and remission no earlier than two weeks of steroid therapy. Finally, non-demonstrated specific onset-related risk factors for NS relapse were considered: hypertension, reduced eGFR, thrombocytosis, and hematuria. Statistical analysis was performed through R 4.3 (R Foundation for Statistical Computing, Vienna, Austria). All tests were 2-tailed, and a p-value less than 0.05 was considered statistically significant. Continuous numeric variables were summarized as mean, standard deviation (SD), or median and interquartile range (IQR), and categorical variables were summarized as absolute and relative frequency (percentcent). The point estimate of the prevalence of FR, SD, and NFRNSD SN subtypes was targeted by a 95% confidence interval (95% CI). Associations between numerical variables were evaluated with Pearson’s correlation coefficient. When there was a statistical association, the effect of known and unknown risk factors for relapses on the variables of interest was reported as a regression coefficient with 95% confidence interval (95% CI). Given the limited number of patients and the absence of the totality of data from all patients in some determinations, some associations were performed using Fisher’s exact test to compare demographic and onset-related risk factors with the characterization of the specific patient in a specific NS subtype.

Results

This study involved 49 patients (31 males, 18 females). The mean age of onset of primitive NS was 3.94 years. 79.5% had at least one episode of NS relapse during follow-up. 69.4% of the subjects were affected by FR or SD NS. The prevalence of risk factors for NS relapse and the association with classification into FR, SD, and NFRNSD subtypes is shown in Table 1. Specifically, the most represented risk factors were represented by male gender, non-Western ethnicity and age less than 5 years old, hypoproteinemia and hypoalbuminemia and remission within 2 weeks at the time of the onset of NS. Children with non-Western ethnicity have a higher risk of developing NS-relapse and being classified into SD NS subtype ($p = 0.041$). Moreover, thrombocytosis at the onset of NS is associated with fewer relapses classification into NFRNSD NS subtype ($p = 0.03$); simultaneously, these patients seem less likely to develop both SD SN ($p = 0.03$). Male sex, age < 5 years, reduced serum albumin and serum total proteins, remission no sooner than two weeks of steroid therapy, arterial hypertension, kidney failure, and hematuria were not associated with more relapses and classification into a specific subtype of NS.

Risk factors for Nephrotic Syndrome relapse	Population (n, %)	FR NS	SD NS	NFRNSD NS
Sex	Males 31 (63.3%) Females 18 (36.7%)	NS	NS	NS
Ethnicity	Non-Western 31 (63.3%) Western 18 (36.7%)	NS	**0.041**	NS
Age < 5 years old	Yes 36 (73.5%) No 13 (26.5%)	NS	NS	NS
Total serum protein < 4.2 g/dL	Yes 27 (65.8%) No 14 (34.2%)	NS	NS	NS
Albumin < 1.8 g/dL	Si 22 (52.3%) No 20 (47.7%)	NS	NS	NS
Remission no sooner than two weeks of steroid therapy	Yes 13 (28.3%) No 33 (71.7%)	NS	NS	NS
Arterial hypertension	Yes 7 (20%) No 28 (80%)	NS	NS	NS
Kidney failure	Yes 1 (2.9%) No 34 (97.1%)	NS	NS	NS
Microhematuria	Yes 20 (48.8%) No 21 (51.2%)	NS	NS	NS
Thrombocytosis	Yes 8 (28.6%) No 20 (71.4%)	NS	NS	**0.030**

Table 1. Association between risk factors for NS relapses and NS subtypes. Values are expressed as p-values. FR: frequent relapsing. SD: steroid-dependent. NFRNSD: non-frequently relapsing non-steroid-dependent.

Discussion

The identification of risk factors for NS relapses is important in the prognosis of idiopathic primary NS because the number of relapses is related to adverse effects due to prolonged exposure to steroids and the use of steroid-sparing agents used in FR and SD NS subtypes [1]. Our study demonstrated that the specific risk factors “non-Western ethnicity” is related to the likelihood of developing more relapses of NS, SD subtype and worse prognosis. This finding confirms the previous evidence regarding the emerging role of genetic factors in the pathogenesis of NS [1]. At the same time, it is known that thrombocytosis can be often observed in subjects with onset of NS [9, 10]. On the other hand, controversial evidence deepened the role of thrombocytosis as a favourable or unfavourable risk factor for the prognosis of NS. Hafni et al. [11] tried to deepen the possibility of an association between thrombocytosis and NS relapses, demonstrating that it is more frequent in FR NS subtype. The assessment of thrombocytosis as a “favourable” prognostic factor has never

been demonstrated in the literature and should be interpreted cautiously. The explanation for this phenomenon seems to be related to both circulating systemic factors and immune system dysregulation, with similar transcriptional and cytokine pathways involved in increased platelet counts and relapse of NS [12, 13]. This study is subject to multiple limitations. First, the small sample size. Second, it is a single-centre study. Third, the data were collected from a database, so there is a risk that some of the data may have been misclassified. Finally, not all variables were recordable for all patients involved in the study. The evidence demonstrated in our study could support the follow-up of NS and be used as the basis for clinical trials to develop targeted algorithms for specific risk factors for relapses.

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