Research Article

The Prevalence of Low Birth Weight in Children with Nephrotic Syndrome

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Abstract

Background: Nephrotic syndrome (NS) is a common disease in children with many consequences for their health, particularly when the disease is severe, accompanied by frequent recurrences, and must be treated with high-dose, long-term corticosteroids.
Objectives: We aimed to determine the effect of birth weight on complete response to corticosteroids in children with NS.
Methods: Two hundred and ninety-two children with NS aged 1 - 18 years were included in the present cross-sectional study. The children followed up from 2010 to 2021 at Ali-Ibn-e-Abitaleb Hospital, Zahedan, Iran. Data were obtained by reviewing medical records for results and completing a parental self-reported questionnaire for birth-related information. For the analysis, SPSS 23 was applied with P < 0.05 as a significance level.
Results: In the steroid-resistant (28.9%) group, low birth weight (LBW) was significantly higher than in the steroid-sensitive (10.5%) group (P = 0.001). A two-way logistic regression report showed that birth weight (P = 0.04, OR = 0.58, 95% CI: 0.34 - 0.99) and number of recurrences (P = 0.001, OR = 4.60, 95% CI: 2.91 - 7.27) were both significantly associated with the development of steroid resistance.
Conclusions: In patients with NS, there was a significant association between LBW, higher relapse rates, steroid resistance, and thus poorer patient outcomes.

Keywords: Birth Weight, Nephrotic Syndrome, Steroid-Resistant Nephrotic Syndrome

1. Background

Nephrotic syndrome (NS) is the most common kidney disease in children, affecting 1 to 17 out of every 100,000 children annually (1). In children, the diagnostic criteria for NS include edema, hypoalbuminemia (less than 3 g/dL), proteinuria (more than 40 mg/m²/h), and hypercholesterolemia (more than 250 mg/dL) (2, 3). Nephrotic syndrome is transmitted by both genetic and environmental factors (3, 4). Additionally, immune system dysfunction that destroys the renal filtration barrier could cause NS. Tumor necrosis factor (TNF) and transforming growth factor (TGF) are the starting points for NS and are progressed by the deposition of immune complexes and autoantibodies against the basement membrane. Overactivity of T-cells (CD8 and T helper 1 and T helper 2) is conducted to increase levels of inflammatory cytokines (interleukin 1, IL4, 2, 12, 18) (5).

Several diseases are associated with NS, but minimal-change nephrotic syndrome (MCNS) is the most common type (6). It is still difficult to draw a conclusion about NS prognosis and clinical consequences. Every NS case received empiric corticosteroid therapy due to the 90 - 95% treatment response rate for MCNS, the most common type of NS in children (7). Nephrogenesis occurs in utero between 34 and 36 weeks of gestation. Sixty percent of nephrons promote during the third trimester, putting premature infants at significant risk for inadequate kidney growth. An adjusting reaction to increasing distinct nephron glomerular filtration rate occurs when the number of nephrons decreases in low birth weight (LBW), resulting in decreased glomerular filtration surface area. Early-onset renal disease is brought on by glomerular filtration abnormalities and damaged podocytes (8). This reaction then raises the risk of developing kidney damage and type of illness (9, 10). Hypertension (11), obesity (12),

renal disease ([13]), cardiovascular disease ([14]), and other chronic diseases are all linked to LBW. Several studies have shown that patients with LBW have more relapses and steroid-resistant nephrotic syndrome (SRNS) ([8]). According to previous studies investigating the effect of birth weight on the consequences of NS, the response to a corticosteroid regimen in NS is the most important prognostic factor. These studies also found that children with higher rates of LBW had an exacerbated course of NS ([14]), which, in some studies, was lower in the LBW group than in the group with normal birth weight (NBW).

2. Objectives

The present study was designed because NS has many causes, including genetic and environmental etiologies, and according to contradictory studies on the effect of LBW on the incidence of NS and treatment response, as well as the frequency of LBW babies in Sistan and Balouchestan province.

3. Methods

Two hundred and ninety-two children with NS aged 1 to 18 years were considered for the present cross-section study. The children were followed up at Ali-Ibn-e-Abitaleb Hospital in Zahedan, Iran, from 2010 to 2021. Some of these profiles were excluded from the study due to missing data based on their mother's reports. Children with nephrotic conditions at birth, a disease affecting multiple organs, or other causes of NS were also excluded. The missing data were related to birth weight, diagnosis date, or gestational age (total of 33 children). After excluding these children from the study, 259 were analyzed.

Nephrotic syndrome is characterized by nephrotic-range proteinuria and either hypoalbuminemia (serum albumin < 30 g/L) or edema when serum albumin level is not available ([1]). Complete remission within 4 weeks of prednisone or prednisolone at the standard dose (60 mg/m^2/day or 2 mg/kg/day, maximum 60 mg/day) is known as steroid-sensitive nephrotic syndrome (SSNS). Lack of complete remission within four weeks of treatment with prednisolone at standard dose is called SRNS ([2]). We defined relapse as having less than 3.0 g/L of protein in the urine for three consecutive days, necessitating the use of steroids, which led to an increase in the dose. The definition of frequently relapsing nephrotic syndrome (FRNS) was less than two relapses within six months of the disease or less than four relapses in a given year. The results of paternal self-reported questionnaires regarding birth-related information were accessed via medical chart review. The World Health Organization (WHO) defines LBW as a child born weighing less than 2500 g. As a result, children were deliberately given an NBW if they were born weighing 2500 g. The present research was approved (code: IR.ZAUMS.REC.1399.377) by the Ethics Committee of the Faculty of Medicine at Zahedan University.

3.1. Statistical Analysis

The subjects' data are presented in the form of a mean, standard deviation (SD), or proportions (repeatability of group findings). The student *t*-test or the chi-square test is used for statistical analysis. Binary logistic regression was used to explain the relationship between treatment response and independent variables. At P = 0.05, differences are considered statistically significant.

4. Results

We identified 292 children with NS between 2010 and 2021. Of them, 259 meeting the inclusion criteria were registered. For the study duration, each patient received a single dose of corticosteroid (prednisone or prednisolone) at a concentration of two milligrams per kilogram (maximum sixty milligrams) once every four to six weeks for a total of six weeks. A total of 259 children participating in this study were divided into two groups: Steroid-sensitive (n = 162) and steroid-resistant (n = 97). Steroid-sensitive nephrotic syndrome is more common in children than SRNS (62.5% vs. 37.5%). The subjects' mean age at disease was 5.35 ± 2.89 years in the steroid-sensitive group and 6.18 ± 3.67 years in the steroid-resistant group (P = 0.46). Comparing the steroid-sensitive group with the steroid-resistant group indicated that the birth weight was 3.0 ± 0.54 versus 2.77 ± 0.66, respectively (P = 0.005). The two groups' serum levels of cholesterol, triglycerides, albumin, and creatinine were not significantly different. Additionally, the steroid-resistant group had a more significant frequency number than the steroid-sensitive group (1.06 ± 0.65 versus 1.91 ± 0.83; P = 0.001) (Table 1). The study population consisted of 51.7% males and 42.9% females. Low birth weight (< 2500 g) was significantly higher in the steroid-resistant than in the steroid-sensitive group (P = 0.001) (Table 2). Birth weight (P = 0.04, OR = 0.58, 95% CI: 0.34 - 0.99) and number of recurrences (P = 0.001, OR = 4.60, 95% CI: 2.91 - 7.27) were both found to be significantly associated with the development of steroid resistance (Table 3).

5. Discussion

The most prevalent disease in children is NS, which can progress to severe forms that necessitate frequent

Table 1. Demographic and Biochemical Characteristics of Children with Steroid-Sensitive and Steroid-Resistant Nephrotic Syndrome (Independent Sample *t*-Test) [a]

Parameters	All Children	Steroid Responsiveness Status of Nephrotic Syndrome		Significance Level
		Sensitive	Resistant	
Age at diagnosis (y)	5.66 ± 3.22	5.35 ± 2.89	6.18 ± 3.67	0.46
Birth weight (kg)	2.92 ± 0.60	3.00 ± 0.54	2.77 ± 0.66	0.005 [b]
Serum triglyceride, mg/dL	234.09 ± 122.04	223.4 ± 110.64	251.93 ± 137.77	0.085
Serum cholesterol, mg/dL	362.87 ± 112.64	360.32 ± 110.48	367.13 ± 116.60	0.63
Serum albumin, mg/dL	2.40 ± 0.57	2.43 ± 0.59	2.35 ± 0.54	0.27
Serum creatinine, mg/dL	0.72 ± 0.78	0.65 ± 0.61	0.84 ± 1.0	0.092
Weight at diagnosis (kg)	19.45 ± 8.47	18.55 ± 7.40	20.96 ± 9.86	0.38
Number of recurrences	1.38 ± 0.83	1.06 ± 0.65	1.91 ± 0.83	0.0001 [b]

Abbreviation: SD, standard deviation.
[a] Values are expressed as mean ± SD unless otherwise indicated.
[b] P-value < 0.05 is significant.

Table 2. Responses to Steroids by Birth Weight, Age, and Sex (Chi-Square Test) [a]

Parameters	Steroid Responsiveness Status of Nephrotic Syndrome			Significance Level
	Sensitive	Resistant	Total	
Birth weight (kg)				0.001 [b]
Low birth weight	17 (10.5)	28 (28.9)	45 (17.4)	
Normal birth weight	145 (89.5)	69 (71.1)	214 (82.6)	
Total	162 (62.5)	97 (37.5)	259 (100)	
Age at diagnosis				0.039 [b]
Age < 8	129 (79.6)	67 (69.1)	196 (75.5)	
Age > 8	33 (20.4)	30 (30.9)	63 (24.3)	
Total	162 (62.5)	97 (37.5)	259 (100)	
Sex				0.095
Female	63 (38.9)	48 (49.5)	111 (42.9)	
Male	99 (61.1)	49 (50.5)	148 (51.1)	
Total	162 (62.5)	97 (37.5)	259 (100)	

[a] Values are expressed as No. (%) unless otherwise indicated.
[b] P-value < 0.05 is significant.

Table 3. The Odds Ratio for the Development of Steroid Resistance in Relation to Birth Weight and Number of Recurrences

Variables	Odds Ratio	Standard Error	P-Value	95% CI
Birth weight	0.58	0.27	0.04 [a]	0.34 - 0.99
Number of recurrences	4.60	0.23	0.0001 [a]	2.91 - 7.27

[a] P-value < 0.05 is significant.

recurrences and require long-term corticosteroid treatment at high doses [1]. In our study, SSNS is more common in children than SRNS (62.5% vs. 37.5%). Birth weight was higher in steroid-sensitive than in steroid-resistant children (3.0 ± 0.54 versus 2.77 ± 0.66; P = 0.005). According to recent epidemiologic studies, there is a strong correlation between LBW and NS. In these studies, such as Conti et al. [15], steroid resistance risk was found to be significantly linked to LBW, similar to the current study.

Prematurity and LBW were identified as risk factors by Ikezumi et al. [9], suggesting that LBW is more common in children with NS than in healthy children. Sixteen

patients had Focal segmental glomerulosclerosis (FSGS), of which 6 (37.5%) had LBW; this LBW rate was significantly higher than the overall LBW rate in Japan (9.7%). The incidence of LBW was also high in patients with MCNS (12.5%). The majority of patients with MCNS underwent biopsies due to their unfavorable clinical course, which included a significantly high rate of relapse or high reliance on steroid treatment. As a result, the MCNS group had a relatively high incidence of LBW (12.5%), and the findings of other studies suggested that LBW might also be a risk factor for a refractory NS. Although we did not have a control group, these findings are in line with our findings. Teeninga et al. (16) also looked into the possibility of recurrence and steroid resistance in MCNS patients and discovered a significant correlation between LBW and an increased risk of relapse and steroid resistance in patients with LBW. There were 201 MCNS patients investigated in this study, with 176 having an NBW and 25 being underweight. In addition, they demonstrated that individuals with lower weights were significantly more likely to require cytotoxic medications and to develop steroid resistance. However, in accordance with our findings, the LBW group had a higher one-year recurrence rate than the standard birth weight group. Furthermore, Rezavand et al. (17) looked into NS children referring to Imam Reza Hospital to examine the connection between LBW and the likelihood of NS in children and discovered that patients with LBW had twice the risk of developing NS as those with NBW. However, there was no statistically significant difference. Even though their study revealed no statistically significant relationship between NS and LBW, it did reveal that the risk of NS was twice as high in the case group as in the control group. This study was conducted in Iran, the same nation as ours, which may suggest that ethnicity and genetic diversity play a role in the prognostic factors of NS. However, another study in Iran on 54 male and 23 female patients indicated that premature birth did not appear to be associated with the number of recurrences (P-value = 0.99). The birth weight of patients who recurred less than twice and those who recurred more than twice in six months was not significantly different (P = 0.336) using the Mann-Whitney U test. In addition, Fisher's exact test revealed no significant association (P-value = 0.643) between the likelihood of developing steroid resistance and premature birth. In addition, there was no statistically significant relationship between birth weight and steroid resistance (P-value = 0.768) (18), which was not consistent with our findings. Konstantelos et al.'s (8) study investigated 336 children and adolescents with NS, and steroid resistance was shown to be about 3.16 times more likely to occur in LBW children than in NBW children. Our findings are also supported by the

mentioned study's findings. As mentioned previously, NS may be caused by a variety of other factors. As a result, it is recommended that additional research is conducted using larger samples from various ethnic groups. Research has found a connection between the disease course and birth weight and weight gain during the first two years of life. In Plank et al.'s study, there was a higher proportion of those with steroid resistance compared to the children who were considered appropriate for gestational age (AGA), and arterial hypertension exacerbated the disease course (19). Na et al. reviewed the medical records of 56 Korean children with NS and showed that steroid resistance was significantly more prevalent in the small for gestational age (SGA) group in their study (14). Multiple studies have demonstrated that children of varying birth weights have distinct steroid responses, which are consistent with our findings regarding SRNS. The parental self-reported birth weights are one of the present study's limitations. Nevertheless, studies have shown that the accuracy of parental self-reported birth weights can be used for both clinical and epidemiological purposes (14, 19).

5.1. Conclusions

We have shown that LBW harms the course and prognosis of NS in children such that children with LBW have more resistance to treatment and more recurrence. These findings help clinicians and parents in assessing the expected clinical practices. Furthermore, as an additional pathogenic principal in renal disease, perinatal programming needs further investigation.

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Footnotes

Authors' Contribution: S. S. B.: The supervisor for the main concept, data collection, and drafting of the primary version of the study; M. A.: Data collection; S. S.: Data analysis; E. Z.: Drafting the final version of the manuscript.

Conflict of Interests: The authors declare no conflict of interest.

Data Reproducibility: The dataset presented in the study is available on request from the corresponding author during submission or after publication. The data are not publicly available due to belonging to a big database.

Ethical Approval: This study is approved under the ethical approval code of IR.ZAUMS.REC.1399.377.

References

1. Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. *Lancet.* 2018;**392**(10141):61–74. [PubMed ID: 29910038]. https://doi.org/10.1016/S0140-6736(18)30536-1.

2. Trautmann A, Boyer O, Hodson E, Bagga A, Gipson DS, Samuel S, et al. IPNA clinical practice recommendations for the diagnosis and management of children with steroid-sensitive nephrotic syndrome. *Pediatr Nephrol.* 2023;**38**(3):877–919. [PubMed ID: 36269406]. [PubMed Central ID: PMC9589698]. https://doi.org/10.1007/s00467-022-05739-3.

3. Nickavar A, Safaeian B, Sadeghi-Bojd S, Lahouti Harah dashti A. Urine Neutrophil Gelatinase Associated Lipocalin to Creatinine Ratio: A Novel Index for Steroid Response in Idiopathic Nephrotic Syndrome. *Indian J Pediatr.* 2016;**83**(1):18–21. [PubMed ID: 26096867]. https://doi.org/10.1007/s12098-015-1809-0.

4. Hashemi M, Sadeghi-Bojd S, Rahmania K, Eskandari-Nasab E. Association between NPHS1 and NPHS2 gene variants and nephrotic syndrome in children. *Iran J Kidney Dis.* 2015;**9**(1):25–30. [PubMed ID: 25599733].

5. Sadeghi-Bojd S, Hashemi M, Firoozi-Jahanigh M, Rezaei M, Sarani H, Taheri M. Lack of Association Between TNF-alpha rs1800629 (-308G > A) Polymorphism and Nephrotic Syndrome. *Iran J Kidney Dis.* 2021;**1**(2):95–100. [PubMed ID: 33764319].

6. Sadeghi-Bojd S, Zarifi E, Tavakolikia Z, Soleimanzadeh Mousavi SH. Evaluation of Response to Treatment in Children with Nephrotic Syndrome over a 10-Year Period: A Retrospective Study. *Int J Pediatr.* 2021;**9**(1):12877–83. https://doi.org/10.22038/ijp.2020.48169.3880.

7. Pasini A, Aceto G, Ammenti A, Ardissino G, Azzolina V, Bettinelli A, et al. Best practice guidelines for idiopathic nephrotic syndrome: recommendations versus reality. *Pediatr Nephrol.* 2015;**30**(1):91–101. [PubMed ID: 25127916]. [PubMed Central ID: PMC4240913]. https://doi.org/10.1007/s00467-014-2903-7.

8. Konstantelos N, Banh T, Patel V, Vasilevska-Ristovska J, Borges K, Hussain-Shamsy N, et al. Association of low birth weight and prematurity with clinical outcomes of childhood nephrotic syndrome: a prospective cohort study. *Pediatr Nephrol.* 2019;**34**(9):1599–605. [PubMed ID: 30976899]. https://doi.org/10.1007/s00467-019-04255-1.

9. Ikezumi Y, Suzuki T, Karasawa T, Yamada T, Hasegawa H, Nishimura H, et al. Low birthweight and premature birth are risk factors for podocytopenia and focal segmental glomerulosclerosis. *Am J Nephrol.* 2013;**38**(2):149–57. [PubMed ID: 23920104]. https://doi.org/10.1159/000353898.

10. Schreuder MF, Nyengaard JR, Fodor M, van Wijk JA, Delemarre-van de Waal HA. Glomerular number and function are influenced by spontaneous and induced low birth weight in rats. *J Am Soc Nephrol.* 2005;**16**(10):2913–9. [PubMed ID: 16093454]. https://doi.org/10.1681/ASN.2004100875.

11. Zarrati M, Shidfar F, Razmpoosh E, Nezhad FN, Keivani H, Hemami MR, et al. Does low birth weight predict hypertension and obesity in schoolchildren? *Ann Nutr Metab.* 2013;**63**(1-2):69–76. [PubMed ID: 23942014]. https://doi.org/10.1159/000351869.

12. Hughson MD, Douglas-Denton R, Bertram JF, Hoy WE. Hypertension, glomerular number, and birth weight in African Americans and white subjects in the southeastern United States. *Kidney Int.* 2006;**69**(4):671–8. [PubMed ID: 16395270]. https://doi.org/10.1038/sj.ki.5000041.

13. Lackland DT, Bendall HE, Osmond C, Egan BM, Barker DJ. Low birth weights contribute to high rates of early-onset chronic renal failure in the Southeastern United States. *Arch Intern Med.* 2000;**160**(10):1472–6. [PubMed ID: 10826460]. https://doi.org/10.1001/archinte.160.10.1472.

14. Na YW, Yang HJ, Choi JH, Yoo KH, Hong YS, Lee JW, et al. Effect of intrauterine growth retardation on the progression of nephrotic syndrome. *Am J Nephrol.* 2002;**22**(5-6):463–7. [PubMed ID: 12381944]. https://doi.org/10.1159/000065275.

15. Conti G, De Vivo D, Fede C, Arasi S, Alibrandi A, Chimenz R, et al. Low birth weight is a conditioning factor for podocyte alteration and steroid dependance in children with nephrotic syndrome. *J Nephrol.* 2018;**31**(3):411–5. [PubMed ID: 29350347]. https://doi.org/10.1007/s40620-018-0473-7.

16. Teeninga N, Schreuder MF, Bokenkamp A, Delemarre-van de Waal HA, van Wijk JA. Influence of low birth weight on minimal change nephrotic syndrome in children, including a meta-analysis. *Nephrol Dial Transplant.* 2008;**23**(5):1615–20. [PubMed ID: 18065792]. https://doi.org/10.1093/ndt/gfm829.

17. Rezavand N, Seyedzadeh A, Tohidi MR, Seyedzadeh MS, Hookary S, Abdi A. The relationship between low-birth weight and nephrotic syndrome in children. *J Nephropharmacol.* 2017;**7**(1):6–9. https://doi.org/10.15171/npj.2018.03.

18. Ghasemi K, Montazeri S, Mokhtari A. Prognostic Role of Gestational Age and Birth Weight in Nephrotic Syndrome: A Retrospective Cross-Sectional Study. *J Ped Nephrol.* 2021;**9**(3):1–5. https://doi.org/10.22037/jpn.v9i3.34482.

19. Plank C, Ostreicher I, Dittrich K, Waldherr R, Voigt M, Amann K, et al. Low birth weight, but not postnatal weight gain, aggravates the course of nephrotic syndrome. *Pediatr Nephrol.* 2007;**22**(11):1881–9. [PubMed ID: 17874138]. https://doi.org/10.1007/s00467-007-0597-9.