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Short communication

Iron deficiency in proteinuric children with nephrotic syndrome: A cross-sectional pilot study

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ABSTRACT

Massive proteinuria in nephrotic syndrome causes depletion of various proteins. Iron deficiency can occur due to urinary loss of iron, transferrin, and soluble transferrin receptors. We conducted this cross-sectional study of 52 children with proteinuric nephrotic syndrome, aged 1–12 years (mean 7.1 ± 2.7 years). Hemoglobin (Hb), RBC indices (MCV, MCH, MCHC), percentage of hypochromic RBCs (Hypo-He), reticulocyte hemoglobin content (Ret-He), and serum ferritin were examined. Seven (13%) patients had iron deficiency anemia and another 10 (19%) exhibited iron deficiency. A higher proportion of children with steroid-resistant disease had anemia than did steroid-sensitive children ($P = 0.076$). Thus, children with nephrotic syndrome may have iron deficiency (32.7%), which needs to be screened.

1. Introduction

Nephrotic syndrome is a common glomerular disease in children characterized by heavy proteinuria (> 40 mg/m^2/day), hypoalbuminemia (albumin < 2.5 g/dL), and edema. Massive proteinuria results in excessive urinary loss of many proteins and, in turn, an alteration in their serum level. Venous thromboembolism, an increased risk of infection, and dyslipidemia are well-studied complications related to protein loss [1]. Anemia can complicate the condition due to urinary loss of iron, erythropoietin, transcobalamin, transferrin, and soluble transferrin receptors [2]. The data on iron deficiency and iron deficiency anemia in nephrotic syndrome are scarce, especially in iron-deficient endemic regions like India where the prevalence is as high as 70% in children younger than 5 years, and this may complicate or adversely affect overall outcome in this subgroup of children [3]. Hence, we planned the present pilot study to determine the frequency of iron deficiency and iron deficiency anemia and its relation to other disease parameters.

2. Methods

This cross-sectional study was conducted in the Pediatric Nephrology Clinic of a tertiary care hospital in northern India from June 2018 to December 2018. After approval from the Institute Ethics Committee, children aged 1–12 years diagnosed with nephrotic syndrome were assessed for enrolment. All consecutive children with nephrotic syndrome presenting to the clinic were enrolled, if they were in a relapse phase, irrespective of previous response to steroid therapy. Patients were excluded if they had severe wasting and stunting, or had/were receiving iron supplements. Children with other chronic disease such as congenital heart disease or chronic liver disease were also excluded (Fig. 1). Approximately, 2.0–2.5 mL EDTA and plain samples were withdrawn for each case and run on an automated hematology analyzer (Sysmex XN-1000; Japan) for complete blood count (CBC), red blood cell (RBC) indices, and newer RBC and reticulocyte parameters (%Hypo-He and Ret-He) and on an automated chemistry analyzer (Advia Centaur; Siemens) for serum ferritin, respectively.

Considering nephrotic syndrome to be a pro-inflammatory chronic condition, a higher cut-off of serum ferritin was taken as a marker for iron deficiency [4]. In addition, Ret-He and %Hypo-He were noted as adjunct markers for defining iron deficiency as low

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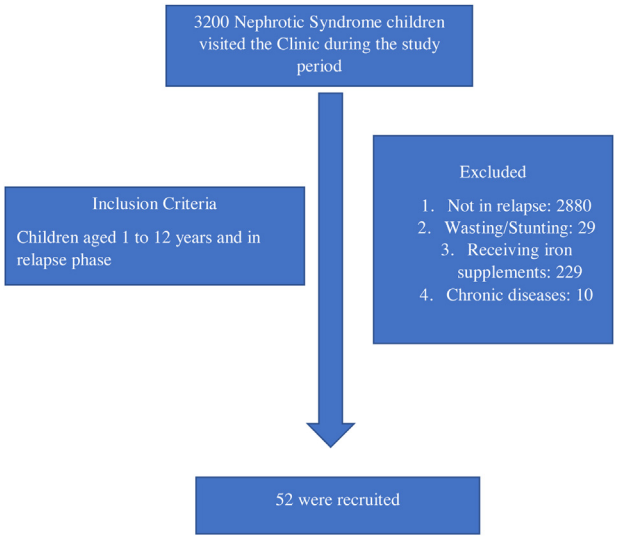

Fig. 1. Flowchart.

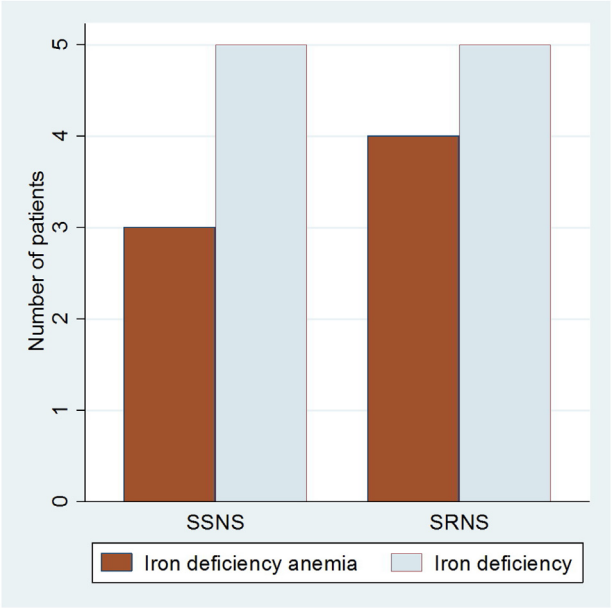

Fig. 2. Frequency of iron deficiency and iron deficiency anemia in children with nephrotic syndrome: SSNS: steroid-sensitive nephrotic syndrome; SRNS: steroid-resistant nephrotic syndrome.

serum ferritin (< 30 mcg/L), low reticulocyte hemoglobin (< 28.6 pg) and high (> 1.6%) hypochromic RBCs [5]. Iron deficiency anemia was defined when, in addition, there was low Hb using age-appropriate cut-offs (Hb < 11.0 g/dL in children aged 0.6–6 years) and Hb < 11.5 g/dL in children aged > 6–12 years) [6]. The patients' demographic profile and disease characteristics were recorded in predesigned case record proforma and statistical analyses were performed using Stata® version 14.2 (Stata Corp, TX, USA).

3. Results

Overall, 52 children with nephrotic syndrome aged 7.1 ± 2.7 years were enrolled in the study. Details of baseline demographic and clinical variables are outlined in Table 1. The median duration of disease in the study children was 2.8 years (interquartile range: 0.8–4.0). All children with a steroid-resistant disease course were on calcineurin inhibitor therapy while 16 patients with steroid-sensitive disease were also taking non-steroid immunosuppressive medications.

Table 1
Baseline characteristics of the study patients ($n = 52$).

Patient characteristics ($n = 52$)	Results
Age at enrolment (years)	7.1 ± 2.7
Age at onset of disease (years)	4.2 ± 2.4
Sex	
Girls	17 (33%)
Boys	35 (67%)
Diagnosis	
Steroid sensitive	37 (71.2%)
Steroid resistant	15 (28.8%)
Biopsy	
Minimal change disease	7 (41%)
Focal segmental glomerulosclerosis	9 (53%)
Others	1 (6%)
eGFR (mL/min/1.73 m^2) mean ± SD	110.4 ± 19.3
Creatinine (mg/dL)	0.21 (0.13–0.30)
Blood urea (mg/dL)	30.6 ± 13
Albumin (g/dL)	2.1 (1.6–2.6)
Cholesterol (mg/dL)	294 (240–356)
Hemoglobin (g/dL)	13.0 ± 1.8

SD: standard deviation; eGFR: estimated glomerular filtration rate.

Low reticulocyte hemoglobin was detected in 24 (44%) children, while hypochromic RBCs were seen in 18 (35%) patients. A total of 19 (36.5%) children had low serum ferritin. However, iron deficiency was noted in 10 (19.2%) children, five each in the steroid-sensitive and steroid-resistant groups. Anemia was detected in 10 (19.2%) children, out of whom seven (13%) patients had iron deficiency and hence iron deficiency anemia. Four (26.6%) patients with steroid-resistant disease had iron deficiency anemia as compared with the three (8.1%) steroid-sensitive patients, although the difference was not statistically significant ($P = 0.07$) (Fig. 2). We did not find any significant association between iron deficiency anemia prevalence and age of disease onset, duration of illness, serum albumin, or creatinine and urine protein excretion (Online materialSupplementary Table S1).

4. Discussion

In our study, we observed that a significant proportion of patients with nephrotic syndrome in a relapse phase had iron deficiency and iron deficiency anemia. Almost 25% of children with steroid-resistant nephrotic syndrome had anemia, while this was diagnosed in less than 10% of patients with steroid-sensitive illness. Although the difference was not statistically significant, this could be explained by prolonged persistent proteinuria in children with steroid-resistant disease resulting in more urinary loss of protein involved in erythropoiesis. This figure may seem low compared with the high prevalence of 70% in the general population [3]. However, almost 70% (229/320) of those with relapse were on iron supplements, as shown in the flowchart.

Although hypochromic RBCs were detected in 35% patients, iron deficiency was diagnosed only in 19% patients as defined based on a combination of low ferritin, high hypochromic RBCs, and low reticulocyte hemoglobin levels. We took this stringent definition of iron deficiency in nephrotic syndrome since it is a pro-inflammatory condition and serum ferritin alone as an iron store marker could be falsely elevated as an acute phase reactant [4]. Hence, a newer reticulocyte parameter (Ret-He), which reflects the acute

availability of iron to bone marrow for erythropoiesis, and %Hypo-He, which reflects chronic availability of iron (over 3 months, considering RBC life span of 120 days) to bone marrow, were included to precisely define the iron deficiency and iron deficiency anemia groups. This study highlights that iron deficiency is common in children with nephrotic syndrome especially in those with a steroid-resistant course hence they should be screened, since persistent deficiency if left untreated is likely to affect their quality of life and cognition.

The prevalence of iron deficiency anemia in nephrotic syndrome has been evaluated in previous studies [2,7,8]. Feinstein et al. studied children with steroid-resistant nephrotic syndrome and normal renal function and they reported that 59% of children had anemia although it was not mentioned if this was iron deficiency. The overall prevalence of anemia in the present study is less than that reported in the study by Feinstein et al., and this difference can be explained by the fact that they studied all children with steroid-resistant nephrotic syndrome. Similarly, Iorember et al. in their review articles reported that at least 28% of children with nephrotic syndrome at their center had anemia during the course of disease. We did not find a significant association between prevalence of anemia and any of the clinical and biochemical parameters in these children with nephrotic syndrome since the sample size was too small in present study.

Urinary loss of iron, transferrin, soluble transferrin receptor, and erythropoietin has been hypothesized to cause anemia in children with nephrotic syndrome during the relapse phase [2,9–12]. Few studies, however, have reported that these children have an elevated level of soluble transferrin receptor, which has been hypothesized to protect against iron deficiency [13,14]. Prinsen et al. have shown that there is an increase in transferrin synthesis, which correlates with albumin synthesis, although again not enough to ameliorate the effects [15]. Although we did not examine the serum and urinary level of iron and transferrin, which is a limitation of the present study, we utilized other surrogate markers of acute and chronic iron-restrictive erythropoiesis including Ret-He and %Hypo-He to define iron deficiency anemia. In fact, Ret-He has been reported to be a specific marker suggestive of iron deficiency anemia in children [5].

Supplementation of both iron and erythropoietin has been suggested by Vaziri in his comprehensive review [16].

5. Conclusion

This pilot study highlights that iron deficiency and iron deficiency anemia are common in children with nephrotic syndrome. Thus, it is suggested that all newly diagnosed and follow-up cases of nephrotic syndrome be routinely assessed (3–6 monthly) for this deficiency using a combination of serum ferritin and technically less cumbersome to perform surrogate CBC markers such as Ret-He and %Hypo-He. However, more studies with a larger sample size are required to prove any relation to disease outcome and other phenotypic features of nephrotic syndrome, treatment received, and whether the deficiency complicates long-term treatment outcome. Moreover, we suggest that once iron deficiency is identified in these patients, they should be promptly treated to avoid delayed adverse outcomes related to iron deficiency.

Status of ethical clearance

Cleared by Institute Ethics Committee (NK/3734/MD886).

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.arcped.2021.05.005.

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