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Iron Deficiency Anemia in Children with Idiopathic Nephrotic Syndrome

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Abstract:

- ***Background***: Anemia is one of the many complications seen in patients with persistent nephrotic syndrome and may occur as a result of excessive urinary losses of iron, transferrin, erythropoietin, transcobalamin and/or metals.
- ***Aim of the study*:** search for iron deficiency in children with nephrotic syndrome.
- ***Patient and method:*** This cross-sectional study included two groups of patients, 40 patients with steroid sensitive and resistant nephrotic syndrome, aged 2-12 year of age, of either sex, who attended Child Central Teaching hospital during the period from June 2018 to April 2019. A thorough full history and clinical examination was done and all patients have been sent for investigation to search for anemia.
- ***Results:*** 35% of patients with steroid resistant nephrotic syndrome were complaining from anemia, while none of patients with steroid responsive had anemia of any cause. There was a significant difference (P= 0.001) between study group in Blood Film results as all patients of responsive group showed normal blood film compared to only seventy-five percent in resistant group.
- **Conclusion:** iron deficiency anemia has been observed to occur in higher frequency in steroid resistant nephrotic syndrome due to difficulty in controlling proteinuria and the continuing iron losses.

INTRODUCTION

Nephrotic syndrome is a common type of kidney disease seen in children. The disease is due to the development of structural and functional defects in the glomerular filtration barrier, resulting in its inability to restrict urinary loss of protein[1]. Complications may occur in nephrotic syndrome as a result of the disease itself as well as its treatment[2].

Mechanisms of anemia in nephrotic syndrome:

- **Altered iron and transferrin homeostasis**

Iron deficiency anemia in nephrotic syndrome has been attributed to increased urinary losses of iron and transferrin. Iron is lost into the urine bound to transferrin, and it remains bound to transferrin in alkaline urine, eventually to be excreted in this state.[3]

- **Urinary losses of erythropoietin**

Erythropoietin has a molecular weight of 30.4 kDa, less than half the weight of albumin, and urinary losses of erythropoietin are expected to be significant in nephrotic syndrome. Thus, erythropoietin deficiency should always be considered to be a contributing factor to the development of anemia in nephrotic patients[4.5,6].

Patients and method:

This cross-sectional study included two groups of patients with idiopathic nephrotic syndrome who were attending to Department of Pediatric nephrology in Child Central Teaching Hospital during the period from first of June 2018 to thirty of April 2019; the first group included were steroid responsive nephrotic syndrome and other group with steroid resistant nephrotic syndrome[7].

A thorough full history had been taken and clinical examination to search for sign of anemia was done and recorded on patient forma.

Basic biochemical and hematological investigation to evaluate general condition during follow up and to search for iron deficiency anemia and the causes of anemia had been done to all patients in both groups, GUE, stool for occult blood, 24 urinary protein excretion, in case of SRNS, S. albumin, S. cholesterol, TSPRFT; blood urea and serum creatinine, CBC, blood film, reticulocyte count, serum iron, serum ferritin, serum transferrin, TIBC, CRP.

Exclusion criteria:

1- Patients with possible secondary causes of nephrotic syndrome.

2- Age <2 year or > 12 year at time of diagnosis.

3- Patients with abnormal renal function test.

4- Patient diagnosed before or during the study as having anemia of any cause.

5- Patient send for stool analysis for parasite, ova and send for stool for occult blood to exclude those with iron loss through stool.

6- Patient send for CRP to exclude infection causing high serum ferritin as an acute phase reactant.

7- Patient with gross hematuria were excluded from the study, as it may be the cause of iron deficiency.

8- Patient with steroid responsive nephrotic syndrome were treated with prednisolone according to standard protocol, 60mg/m^2/day for 6 weeks, followed by 40 mg/m^2/day on every alternate day for the next 4 weeks after achieving remission then tapered gradually. while patient with steroid resistant nephrotic syndrome where treated after they complete 6 weeks of for full dose (60 mg/m^2/day) and when they didn't respond

they are given three doses every other day pulse methylprednisolone, then the prednisolone tapered to (40mg/m^2/day) every alternate day the next 4 weeks then tapered gradually, other patients in steroid resistant group had received prolonged course of high dose pulse methylprednisolone (Mendoza protocol)[9], others received every other day dose oral steroid for prolonged period more than six months[8].

9- We selected the patients those who didn't take immunosuppressive, most the patients with SRNS enter the study before renal biopsy.

RESULTS

Study patient's age was ranging from 2 - 12 years with a mean of 7.25 years and a standard deviation (SD) of ± 2.94 years. The highest proportion of study patients in sensitive and resistant groups was aged ≥ 6 years (70% and 55% respectively),

Regarding gender, in sensitive group proportion of males was equal to that of females (50% versus 50%), while in resistant group, proportion of males was higher (60% versus 40%).

There were no significant differences ($P \geq 0.05$) between study groups in means of RBC count, RDW, retics, TIBC, s. transferrin and s. ferritin.

Clinical Parameters	Study Group		P-Value
	SSNS Mean ± SD	SRNS Mean ± SD	
TSP (g/dl)	62.65 ± 9.53	38.05 ± 5.78	**0.001**
S. Albumin (g/dL)	40.25 ± 8.32	16.51 ± 3.07	**0.001**
Urinary protein excretion (mg/m^2/hour)	2.6 ± 0.4	68.4 ± 15.8	**0.001**
S. Cholesterol (mg/dl)	5.65 ± 3.54	10.27 ± 2.57	**0.001**
RBC Count (cells/mcL)	5.17 ± 0.27	5.1 ± 0.78	**0.718**
RDW (%)	11.47 ± 1.27	12.38 ± 1.6	**0.056**
PCV (%)	41.76 ± 3.42	36.18 ± 7.26	**0.004**
Hb (g/dl)	14.33 ± 0.99	12.29 ± 2.83	**0.004**
MCV (fL/red cell)	80.29 ± 5.03	71.44 ± 8.17	**0.001**
MCH (pg/cell)	28.75 ± 1.25	24.97 ± 3.72	**0.001**
MCHC (g/dL)	36.24 ± 1.24	33.68 ± 2.71	**0.001**
Retics (%)	1.84 ± 0.79	1.76 ± 0.96	**0.79**
S. Iron (µg/dL)	84.49 ± 34.99	60.99 ± 26.25	**0.021**
S. Ferritin (ng/mL)	78.8 ± 33.47	48.68± 94.76	**0.188**
TIBC (mcg/dL)	333.47 ± 111.16	380.79 ± 126.27	**0.216**
S. Transferrin (mg/dl)	436.17 ± 634.51	229.77 ± 64.44	**0.156**
Transferrin saturation (%)	29.44 ± 14.47	20.58 ± 11.98	**0.042**

Table 2: Distribution of study patient according to the presence of anemia and type of anemia

	Responsive n= 40	Resistant n= 40	
No	40 (100.0)	26 (65.0)	66 (82.5)
Iron deficiency Anemia	0 (0)	10 (25.0)	10 (12.5)
Other types of anemia	0 (0)	4 (10.0)	4 (5.0)

Table (3) shows the Blood Film results among study groups. There was a significant difference (P= 0.001) between study group in Blood Film results as all patients of sensitive group showed normal blood film compared to 75% in resistant group.

Table 3: comparison between study group by Blood Film result

Blood Film Result	Study Group		Total (%)	P- Value
	Responsive n= 40	Resistant n= 40	n= 80	
Hypo	0 (0)	10 (25.0)	10 (12.5)	0.001
Normal	40 (100.0)	30 (75.0)	75 (87.5)	

There is a significant moderate positive correlation between s. albumin and both of s. iron, and transferrin saturation (r = 0.426, P= 0.006; and; r = 0.463, P= 0.003 respectively), while there is a significant weak negative correlation between s. albumin and s. ferritin (r = - 0.368, P=0.019) as shown in figure (3.4, 3.5 and 3.6).

Regarding retics, TIBC and s. transferrin there were no significant correlations ($P \geq 0.05$) noticed with s. albumin.

Table 4: Correlations between s. albumin and certain clinical parameters

Clinical Parameters	S. Albumin (g/L)	P - Value
	R	
Retics (%)	0.233	0.148
S. Iron (µg/dL)	0.426	0.006
S. Ferritin (ng/mL)	- 0.368	0.019
TIBC (mcg/dL)	- 0.182	0.262
S. Transferrin (mg/dl)	0.254	0.124
Transferrin saturation (%)	0.463	0.003

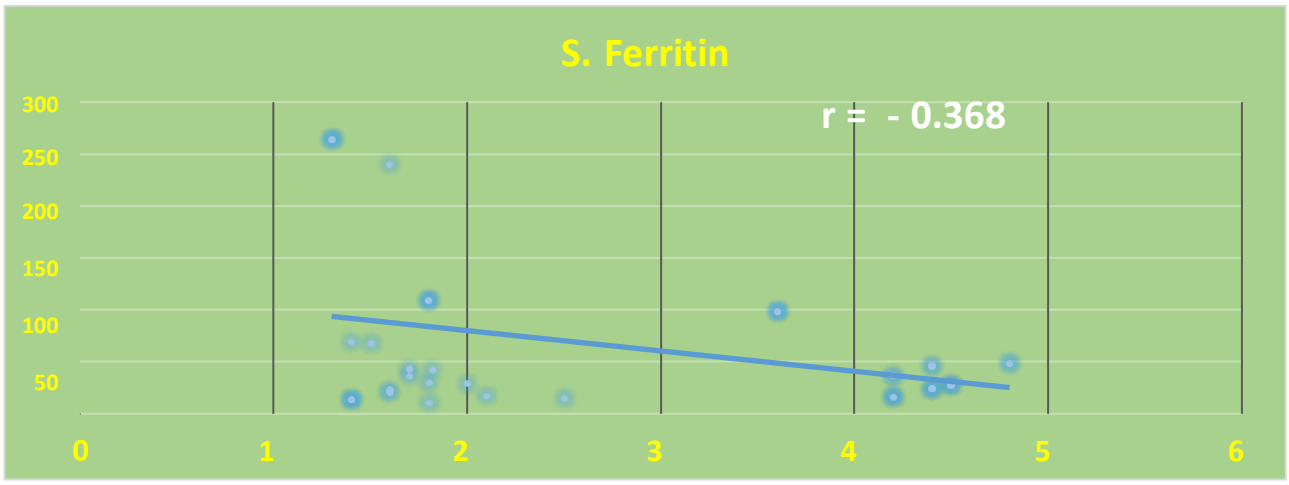

Figure 1: Correlation between s. albumin and s. ferritin.

DISCUSSION

Anemia due to iron deficiency has been observed in both adults and children with idiopathic nephrotic syndrome before the deterioration in kidney function. In our study we found that 35% of our patients with steroid resistant nephrotic syndrome have anemia (25% having iron deficiency anemia and 10% have other causes of anemia) while none of our patients with steroid sensitive nephrotic syndrome have anemia and this result correlates with that of Feinstein et al [10] which showed a prevalence of 59% of patients with idiopathic nephrotic syndrome having anemia, most of them having steroid resistant nephrotic syndrome. This is consistent with the result of Iorember et al[2] where approximately 28% of their patients have anemia during the course of their illness.

A common denominator in these anemic patients is the persistent or therapy-resistant nature of their nephrotic syndrome. Although the pathophysiologic mechanisms of anemia of chronic

kidney disease are well established[9,] the mechanisms of anemia in nephrotic syndrome in the setting of normal renal function are complex and incompletely understood.

The mean age of our patients was 7.25 years ± 2.94 years, this was near that of Feinstein et al(30) where it was 6 years ± 1.1 and similar of that of Pokrajac et al[11] which was 7.5 ±4.5, while Eddy et al[(12)] compare type of nephrotic syndrome where it showed 70% of MCNS patients are younger than five years; 20-30% of adolescent nephrotic patients have MCNS.

Our study didn't show a positive correlation with age of the patient and the development of anemia, but we found that the age is a significant contributing factor in the assessment of proteinuria in resistant group as urinary protein was significantly higher among age group <6 years than that in age group ≥ 6 years (3.88 versus 3.45, P= 0.045) and as a result the mean of TSP, s. albumin and transferrin saturation was significantly higher among patients aged ≥ 6 years than that in patients aged < 6 years (40.81 versus 34.66, P= 0.013; and 17.92 versus 14.77, P= 0.018; and 25.92 versus 14.06, P= 0.023 respectively). This may be explained by the fact that urinary protein loss in adult with nephrotic syndrome, in relation to the weight, was much less than in children.

The duration of disease might have important influence on the development of iron deficiency anemia as discussed in Iorember et al [2] and Brown et al [13] but we couldn't assess this fact exactly as 85% of our patient with steroid resistant group had nephrotic syndrome less than five years. Feinstein et al [5] showed that duration to cause anemia 3.9 months ±1.2 but we couldn't assess this result as we couldn't follow our patients during a period of time.

In our study, we found out that mean of TSP, s. albumin and transferrin saturation was significantly become higher as the duration of illness was longer in patient with steroid resistant (42.44 versus 34.45, P= 0.001; 18.35 versus 15.0, P= 0.011; and 26.78 versus 15.51, P= 0.032

respectively), this could be explained as that as the prolonged exposure to proteinuria causing renal damage and fibrosis which in turn decrease proteinuria and subsequently increase TSP, s. albumin and transferrin saturation.

Anemia in cases of idiopathic nephrotic syndrome may be attributed to many mechanisms; it can be attributed to increasing iron loss in urine as found in Brown et al [13] with six of nine of their patient in INS had increase urinary iron, we couldn't search for this value because of the lack of facilities in our laboratory. Meanwhile, we searched for the level of serum iron which showed higher value in sensitive group than in resistant group (84.49 versus 60.99 P=0.021) and this correlates with Feinstein et al[5] and Lu et al [13] where serum iron is significantly lower in nephrotic syndrome during relapse and this may be indirect indicator that persistent proteinuria means persistent iron loss. Serum ferritin reflects tissue iron store and it is a sensitive parameter for iron deficiency[16], Feinstein et al[5] showed serum ferritin significantly lower in group of anemia and nephrotic syndrome, our study showed no significant difference in both study group regarding to serum ferritin (78.8 versus 48.6 P=0.188) and this agrees with that of Lu et al [14]. The mechanism leading to high level of ferritin remains unknown. Studies have documented that synthesis and transportation of ferritin were increased in patients with renal disease, and that the increase in ferritin is partially the result of increased synthesis of non-specific hepatic proteins[15, 18], it may be explained also by the fact that ferritin is a large molecular weight protein, and little is excreted from the urine in INS so as a result the serum level of ferritin remained normal[14]. Our study, showed no significant differences in serum transferrin between both study groups (436.17±634.51) (229.77±64.44) and this disagree with that of Lu et al[13] which showed a decrease level of serum transferrin in cases of idiopathic nephrotic syndrome during relapse and this can be explained by the fact that the synthesis of transferrin was increased, the rate of

synthesis was slower than that lost from the urine because the molecular weight of transferrin is similar to that of albumin, which may in turn explain decrease transferrin level in serum[17].

Meanwhile, transferrin saturation is significantly lower in group SRNS than in SSNS (20.85 versus29.44 p=0.042) and this correlate with Feinstein et al[(5)] and Lu et al [(13)] which showed that transferrin saturation was higher in those of healthy control and those at remission stage.

Our study showed no significant difference (P> 0.05) in measure of TIBC and this disagree with that of Feinstein et al [(5)] which showed TIBC tended to be lower in their study group of NS with anemia, this may be explained by the difference in sample size.

S. albumin showed significant difference between sensitive (40.25±8.32g/dL) and resistant (16.51±3.07g/dL) with (P value 0.001) and this result correlate with that of Feinstein et al[(5)] which show low serum albumin in group with nephrotic syndrome and anemia. We also find a moderate positive correlation between serum albumin and that of serum iron (P=0.006) and transferrin saturation (p = 0.003) and there is significant weak negative correlation between s. albumin and s. ferritin (p = 0.019).

CONCLUSION

1. Iron deficiency is one of the possible complications in case of nephrotic syndrome and this may be severe enough to cause iron deficiency anemia.
2. The frequency of iron deficiency anemia is higher in cases of steroid resistant nephrotic syndrome due to difficulty controlling proteinuria and the continuing iron losses.
3. Serum iron correlates with serum albumin.

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