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The Relationship between Blood Biomarkers Level and the Prognosis of Nephrotic Syndrome in the Children

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Abstract

Background

Nephrotic syndrome (NS) characterized by a large amounts of protein into urine and a set of indications that include: protein in urine, low blood protein levels, high cholesterol levels, high triglyceride levels, and swelling. Therefore, aim of this study was to investigate the relationship between prognosis of nephrotic syndrome and blood biomarkers level in children of Arak city, Iran.

Materials and Methods

This was a prospective study of case series patients which conducted on 100 children with nephrotic syndrome referred to the pediatric clinic in Arak-Iran durring 2015 to 2016, to determine the resistance to steroids initially. All children had been taking Prednisolone and then, they were divided into four groups based on response to steroid. Also, blood biomarkers obtained from interviewing. Data were analyzed using SPSS-21.

R***esults***

Results showed that children with steroids responded nephrotic syndrome rather than frequent relapse nephrotic syndrome, steroid resistance nephrotic syndrome and steroids dependent nephrotic syndrome patients had lower blood inflammatory and higher blood anti-inflammatory markers and there was a significant difference between these markers ($P<0.05$).

Conclusion

A number of inflammatory factors were lower than normal in responded group and number of anti-inflammatory factors was higher than normal in responded group. Therefore, in treatment of children, these inflammatory and anti-inflammatory factors should be controlled.

Key Words: Blood Biomarkers, Children, Nephrotic syndrome.

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1- INTRODUCTION

Nephrotic syndrome which also known as the nephrosis in medicine and urology has set of signs and symptoms that are caused by damage to the glomerular basement membrane as to result increased glomerular permeability is due to alterations in the normal glomerular cellular and basement membrane barrier and then kidney excreted large amount of protein into the urine (1). Although, kidney of healthy children has as low as urinary protein excretion (<4 mg/m2/hour or uP/Cr <0.2), but in this syndrome, urinary protein excretion increases and reaches more than 40 mg/m2/hour or U PR/Cr >2.0 and proteinuria between these levels is mildly to moderately elevated but not nephrotic syndrome. In particular, the albumin protein in the urine, leading to persistent heavy proteinuria (mainly albuminuria) (>2 g/m2/24 h); hypoproteinemia (serum albumin <3.0 g/dL); hypercholesterolemia (>250 mg/dL); and edema because of plasma oncotic pressure is diminished, leading to fluid shifts from vascular to interstitial compartments and plasma volume contraction(2).

On the other hand, renal blood flow and the glomerular filtration rate are not usually diminished. Therefore, edema results from reduction in effective circulating blood volume and increase in tubular sodium chloride reabsorption secondary to activation of the renin–angiotensin–aldosterone system (RAAS). Also, hypoproteinemia stimulates hepatic lipoprotein synthesis and diminishes lipoprotein metabolism, leading to elevated serum lipids (cholesterol, triglycerides) and lipoproteins, thus various symptoms were occurred (3).

In a division that has been done for nephrotic syndrome this syndrome is divided into transient, persistent, asymptomatic, symptomatic, orthostatic (present in the upright position but not in the recumbent position) and fixed (present in all positions) in types by another division, this syndrome can be glomerular (glomerular barrier were destroyed) or tubular (increased filtration, low tubular reabsorption, or secretion of proteins). In a principled classification NS may be primary or secondary. Secondary NS may result from many different causes in children which contains these: systemic lupus erythematosus, Henoch-Schonlein purpura, Wegener and other vasculitis's, chronic infections (hepatitis B, hepatitis C, malaria, human immunodeficiency virus), allergic reactions, diabetes, amyloidosis, malignancies, congestive heart failure, constrictive, pericarditis, renal vein thrombosis and other causes. But primary NS, prior to renal biopsy, is considered to have idiopathic nephrotic syndrome and then divided into different types which contains:

- Minimal change nephrotic syndrome (MCNS) that is the most common histologic form of primary NS in children,
- Focal segmental glomerulosclerosis (FSGS) accounts for approximately 10% to 20% of children with primary NS,
- Membranoproliferative glomerulonephritis (MPGN) is characterized by hypocomplementemia with signs of glomerular renal disease,
- Membranous nephropathy represents less than 5% of children with primary NS,
- Congenital NS presents during the first 2 months of life (2).

About the complications of this syndrome we can see:

- an increased incidence of serious infections, particularly bacteremia and peritonitis, is due to urinary loss of immunoglobulins and complement,
- side effects of steroids are most common in steroid-dependent and frequently relapsing patients and

hypovolemia may result from diarrhea or diuretic use,

- loss of coagulation factors, antithrombin, and plasminogen may lead to a hypercoagulable state with a risk of thromboembolism (TE)(4).

Therefore, prognosis of this syndrome dependent on its type so that the total remission is about 80%, but the worst prognosis is related to the MCNS who nearly 80% of children with MCNS experience NS relapse (5). The nephrotic syndrome has high prevalence in the children's who followed by many complications that are affected by types of syndrome. But no study has been done to investigate this issue prospectively. So, the aim of this study was survey of children with nephrotic syndrome in Arak city who perhaps we can reduce NS and its complications in the community by considering these inflammatory and anti-inflammatory factors in prognosis of syndrome. So that we hypothesized that specific, identifiable clinical blood variables would predict the risk for NS in these children. To test our hypothesis, we conducted a metacentric chart review of a number of children's diagnosed with NS in an attempt to identify these blood factor variables in childrens.

2- MATERIALS AND METHODS

This research was a hospital-based study and patients were selected by convenience sampling. Patients were comprised of children referred to the Amirkabir hospital, Arak city, Iran during 2015-2016 with nephrotic syndrome diagnosis who have urinary protein excretion more than 40 mg/m2/hour or U PR/Cr >2.0. The patients were selected on the basis of this criteria that inclusion criteria were: Age < 18 year, absence of another congenital kidney disease, consent to participate in research projects and exclusion criteria were: severe liver, kidney or cardiac disease, by any reason patient leave the study and not satisfied to use their personal data in the study.

2-1. Measurements

All tests conducted and assessed for all participants for detection of blood markers level. On admission to the hospital blood sampling was done from children in a sitting position and by unit nurses. Blood biomarkers of patients were obtained by serum analysis. About different levels of blood markers, which was determined by serum analysis, and diagnostic standard patients divided into three categories: normal, higher than normal and lower than normal based on the values which provided for these biomarkers.

About response to steroid children were divided into 4 groups, based on their responses to treatment with corticosteroids, responding to steroids, frequent relapse, steroid resistance and steroid dependent. Upon the completion of project blood factors who were examined in patient (Cho, C-reactive protein (CRP), Na, hemoglobin, white blood cell count**,** Red blood cell count**,** hematocrit**,** mean corpuscular volume**,** mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration**,** Red blood cell distribution width**,** platelet count**,** mean platelet volume**,** platelet distribution width**,** procalcitonin, neutrophil, lymph, monocyte, and eosinophil, basophile) were compared together in four groups.

2-2. Ethics

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. Also, the study protocol was approved by the ethical committee of Arak University of Medical Sciences.

2-3. Statistical analysis

Sample size was determined according to previous studies(1, 3, 6) and taking into account the standard deviation equal to 11

standard deviation (SD), 95% confidence level (CI) and 90% power assuming and by using PASS NCSS software 90 was calculated for minimum sample size. Also, by taking into account the loss of about 10% of samples, we included 100 children with nephrotic syndrome diagnosis in patient group. On the other hand, data analysis was conducted by fisher exact, ANOVA and Chi-square test, using SPSS version 21 software and significance level considered for significant difference in groups ($P<0.05$).

3- RESULTS

About demographic information we have examined this information's and then compared them in four groups. About gender of children we observed that difference in four groups is significant (P=0.004). So that in males group were 24% steroid responded, 52% frequent relapse, 52% steroid resistance and 76% steroid dependent and in females group 76% steroid responded, 48% frequent relapse, 48% steroid resistance and 24% steroid dependent. About age of children we compared the average of age in 4 groups and significant difference was observed (P=0.001). Also, we investigate residence status of children and their families in our study and observed that in families with a private home, 76% steroid responded, 68% frequent relapse, 40% steroid resistance and 32% steroid dependent and families who were not in a private home 20% steroid responded, 32% frequent relapse, 60% steroid resistance and 60% steroid dependent. So, we have significant difference in four groups (P=0.02). (**Table-1**).

All blood biomarkers were reviewed by Chi-square test and following results were observed about them. By measuring WBC, it was observed that WBC as an inflammatory factor in steroid responding group, no one was higher than normal, 4% lower than normal and 96% normal and in the three next groups in average 36% higher than normal, 4% lower than normal and 60% normal and this represents that there was significant difference in four groups (P=0.001).

White blood cells component counting showed that monocyte only in steroid resistance group were 4% lower than normal, 96% normal and in another groups appeared perfectly (100%) normal, also about lymphocyte viewed that in responding to steroids group 8% lower than normal and 92% normal and in three other groups 33% lower than normal, 3% higher than normal and 64% normal (P=0.003); so, difference was significant. Also, neutrophil count showed that there was a difference between two groups (SRNS versus FRNS, SDNS and SRNS)(P=0.005). But about basophile and eosinophil we observed that these two cell count were normal in all 4 groups and there was no difference between four groups. Also, about PLT, we observed that there was a significant difference between two groups (SRNS versus FRNS, SDNS and SRNS) (P=0.001), so that in steroid responded group 92% normal, 8% higher than normal and no one was lower than normal, but in another tree groups 26% normal, 70% higher than normal and 4% lower than normal. In lipid profile about cholesterol biomarker we observed that high range of cholesterol amounts in SRNS group was more tahn other groups (FRNS, SDNS and SRNS) (P=0.001).

When the presence or absence of CRP in children was evaluated it was found that positive rate of patients in the tree second groups was more compared to respond to treatment group and there was a significant difference in four groups (P=0.002). On the other hand, when we have examined sodium of serum, we have seen a significant difference (P=0.001), low levels of sodium in another three groups rather than steroid SRNS were significantly higher. But about MPV, PCT, PDW, RDW, MCHC, MCH, MCV, HCT, RBC and HGB blood biomarkers we

observed that there was no sufficient difference between four groups (P>0.05) for this blood biomarkers (**Table- 2**).

Table-1: Demographic characteristics of children with Nephrotic Syndrome

Variables		Steroid responded (remission) (n=25)	Steroids dependent (n=25)	Steroid resistance (n=25)	Frequent relapse (n=25)	Total (n=100)	P-value
Gender	Male	24	76	52	52	68	0.004
	Female	76	24	48	48	65	
Age	Mean ± SD	2.09 ± 4.16	2.60 ±7.96	2.09 ± 9.72	1.91 ± 9.64	3.12 ± 7.87	0.001
Residence Status	With a Private Home	76	68	40	3	73	0.02
	Without a Private Home	24	32	60	64	60	

SD: Standard deviation.

Table-2: Details of blood biomarkers percentage in children with Nephrotic Syndrome

Variables		Steroid responded (remission) (n=25)	Steroids dependent (n=25)	Steroid resistance (n=25)	Frequent relapse (n=25)	Total (n=100)	P- value
WBC (%)	Normal	96	72	56	52	۶۹	0.001
	Higher	0	24	44	40	27	
	Lower	4	4	0	8	4	
Cho (%)	250-350 and Lower	72	32	12	8	31	0.001
	350-450	28	40	12	16	24	
	450-550	0	20	32	32	21	
	550 and Higher	0	8	44	44	24	
CRP (%)	Positive	16	60	56	64	49	0.002
	Negative	84	40	44	36	51	
Hgb (%)	Normal	96	80	84	64	81	0.032
	Higher	4	0	4	12	5	
	Lower	0	20	12	24	14	
RBC (%)	Normal	96	76	84	68	81	0.109
	Higher	0	8	0	4	3	
	Lower	4	16	16	28	16	
Hct (%)	Normal	92	76	84	68	80	0.06
	Higher	4	0	0	0	1	
	Lower	4	24	16	32	19	
MCV (%)	Normal	88	76	84	68	79	0.202
	higher	8	24	16	32	20	
	Lower	4	0	0	0	1	
MCH (%)	Normal	92	72	84	68	80	0.126
	Higher	0	4	0	0	2	
	Lower	8	24	16	32	18	

MCHC	Normal	92	76	84	68	80	0.227
	Higher	0	0	0	4	2	
	Lower	8	24	16	28	18	
RDW	Normal	92	76	80	68	79	0.172
	Higher	0	16	16	12	11	
	Lower	8	8	4	20	10	
Plt	Normal	92	40	20	20	43	0.001
	Higher	8	56	80	76	55	
	Lower	0	4	0	4	2	
MPV	Normal	92	44	16	28	45	0.001
	Higher	0	0	4	0	1%	
	Lower	8	56	80	72	54	
Pct	Normal	100	100	100	96	99	>0.05
	Higher	0	0	0	4	1	
	Lower	0	0	0	0	0	
Neutrophil	Normal	92	84	56	52	71	0.005
	Higher	8	16	40	44	27	
	Lower	0	0	4	4	2	
Lymphocyte	Normal	92	84	52	56	71	0.003
	Higher	0	0	8	0	2	
	Lower	8	16	40	44	27	
Monocyte	Normal	100	100	96	100	99	>0.05
	Higher	0	0	0	0	0	
	Lower	0	0	4	0	1	
Eosinophil	Normal	100	100	100	100	100	>0.05
	Higher	0	0	0	0	0	
	Lower	0	0	0	0	0	
Basophile	Normal	100	100	100	100	100	>0.05
	Higher	0	0	0	0	0	
	Lower	0	0	0	0	0	

4- DISCUSSION

This study aimed to consider the relationship between nephrotic syndrome and blood biomarkers in the children. Kidney of healthy children has a low urinary protein excretion (<4 mg/m2/hour or Up/Cr <0.2), but in this syndrome, urinary protein excretion increases and reaches more than 40mg/m2/hour or U PR/Cr >2.0. Many factors affect nephrotic syndrome and these factors can be show themselves by changes in bodily fluid factors, also different blood cells can be having an effect on the process of nephrotic syndrome. On the other hand, the treatment of this disease in advanced stages is difficult. In our study the relationship between nephrotic syndrome and some inflammatory and anti-inflammatory blood factors was significant and these results are seen in a few studies that the most relevant articles will be discussed and compared with our findings: in a study by Takahashi in 2007 that was about triggers of relapse in steroid-dependent, he observed that 442 relapses occurred in 2,499 patients that were 135 E+ (with episodes) and 296 E− (without episodes) relapses. The common cold was

the most common (52%) episode of E+ relapse. These E+ relapses occurred about evenly during the 4 weeks between each follow-up visit; so they concluded that the common cold and school events as well as up-coming hospital visits may trigger relapses in SDFRNS patients (7), however, in our study this criterion has not been studied.

Also, in a study by Bryce in 2009, observed that incidence of TE in primary and secondary childhood nephrotic syndrome were higher than healthy children's, so children's who have NS should be carefully followed for TE, particularly those who are aged 12 years or over years old, positive severe proteinuria, or have a previous TE (8); however in our study this criteria not followed, but another related criteria has been investigated. Özkaya et al. in a study have been checked protein Z (PZ), they observed that PZ decreased in NS along with the other coagulation abnormalities, decreased it may contribute to increased risk of thromboembolic complications in children with NS, also the negative correlation between proteinuria and PZ level suggests possibility of renal PZ loss (9).

Also, in other study, results showed that children had low level of self-care and frequency of re-hospitalization, standard of parents' socioeconomic balance, education and occupation were significant predictors for low self-care (10). In another study by Yousefichaijan, that was about attention deficit hyperactivity disorder in steroid-dependent nephrotic syndrome, it was observed that there was no significant relationship between different types of ADHD in children with SDNS and the control group(11); but this threads were not investigated in our study. Chanchlani in 2016 in an original article about ethnic differences in NS reported that in children with nephrotic syndrome, incidence and response to treatment in NS was varies by ethnicity (6). In the following Chandra Pandey concluded that there was a significant enhancement in HDL, TG, LDL, VLDL & TC, also notable decline in serum protein, serum albumin and globulin in nephrotic patients when compared to controls (3), about our study TC have been investigated and observed that it has been increased in the syndrome, but another aspect of lipid profile had not investigated because of many studies that have been examined it. In an study who was about epidemiology of renal failure expressed that the incidence of RF was above at the PUHC-CDG of Ouagadougou (12).

Another study by Sreenivasa has been done and observed that on their study, urinary tract infection was a common infection accompanying NS, also a high index of suspicion and early institution of appropriate antibiotics will help in attenuating morbidity and mortality (13), but infection and treatment of it has not studied. Mohammed Youssef has observed that IL2R and MDR1 gene expression levels as fast predictive of steroid resistance in nephrotic syndrome by immediate introduction of cytotoxic drugs (14).

Bai in a study in the 2012 concluded that, compared with the control group, the top severity of four proteins, measured using mass-to-charge ratios, were notable increased in the primary NS group (15).

In an study by Feehally et al., results showed that NS was more preponderant in Asian children living in the city of Leicester, and there was an unusually low incidence in non-Asian children within the city (16). About congenital nephrotic syndrome of Finnish type, a study by Huttunen, observed that more than 50% of the children's died before 6 months and none lived longer than 27 months, also a slight increases in blood urea nitrogen or serum creatinine levels occurred in 14 cases, but no one of them had a frank uremia development before death and this increase was also observed in our study.

Infection appeared to be the immediate cause of death in 31% of the cases; 43% no cause of death rather than congenital nephrotic syndrome could be shown. Thrombi in large vessels were found in 11 out of 58 necropsies (17), but in our study has not observed of the dead children.

4-1. Limitations of the study

Was observed several limitations in our study which we were mentioned some of them. The most important limitation was the lack of samples in case group.

Also another limitation was that patients and their parents were uncooperative with investigators. Furthermore, it is recommended that our findings should be confirmed by further studies with attention to severity factors related to NS.

5. CONCLUSION

About blood biomarkers, who in this study were evaluated, we have seen that only some of them show changes so that inflammatory markers such as WBC, neutrophil, PLT and CRP in groups of lack answers to steroid (frequent relapse, steroid resistance and steroids dependent) were more than responded to medication group. But, some of other inflammatory factors such as lymphocytes and MPV were less than normal in un-responded groups. About cholesterol it proved that amount of Cho in three unresponsive to corticosteroids groups were higher than responding to medication group, so having a high cholesterol level can also, be a risk factor for drug resistance.

6- ABBREVETION

- **NS:** Nephrotic syndrome,
- **SRNS**: Steroid-Resistant Nephrotic Syndrome,
- **FRNS**: Frequent Relapse Nephrotic Syndrome,
- **SDNS**: Steroids Dependent Nephrotic Syndrome,
- **SD:** Standard deviation,
- U PR: Urine Protein,
- **Cr**: Creatinine,
- **RAAS**: Renin–angiotensin–aldosterone system,
- **Cho**: Cholesterol,
- **MCNS**: Minimal Change Nephrotic Syndrome,
- **FSGS**: Focal Segmental Glomerulosclerosis,
- **MPG**N: Membranoproliferative Glomerulonephritis,
- **TE**: Thromboembolism,
- **CRP**: C-reactive protein,
- **CI**: Confidence level,
- **MPV**: Mean platelet volume,
- **PCT**: Procalcitonin,
- **PDW**: Platelet Distribution Width,
- **RDW**: Red blood cell distribution width,
- **MCHC**: Mean corpuscular hemoglobin concentration,
- **MCH**: Mean corpuscular hemoglobin
- **MCV**: Mean corpuscular volume,
- **HCT**: Hematocrit,
- **RBC**: Red blood cell,
- **HGB**: Hemoglobin,
- **E+**: With episodes,
- **E−**: Without episodes,
- **PZ**: Protein Z,
- **ADHD**: Attention deficit hyperactivity disorder,
- **LDL**: Low density lipoprotein,
- **VLDL**: Very low density lipoprotein,
- **TC**: Total cholesterol,
- **PUHC-CDG**: Pediatric University Hospital Center Charles De-Gaulle,
- **IL2R**: Interleukin-2 receptor,
- **MDR1**: Multidrug Resistance Gene 1,
- **WBC**: White blood cell,
- **PLT**: Platelet,
- **Na**: Sodium.

6- CONFLICT OF INTEREST: None.

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University of Medical Sciences, Arak, Iran.

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