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Prognostic validity of mean platelet volume in children with nephrotic syndrome

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Abstract
Background: Nephrotic syndrome (NS) is a common childhood chronic kidney disease. Early prediction for the prognosis of the nephritic syndrome have not been determinate yet.
Objective: To evaluate mean platelet volume as a prognostic biomarker in patients with nephrotic syndrome.
Subjects and Methods: This was prospective comparative study. Eighty children were included in this study which was conducted in the period from August 2014 - 28th February 2015 in the pediatric department of El Minia university hospital, Minia, Egypt. Venous blood samples were obtained during active and remission phases of nephrotic syndrome for complete blood count and mean platelet volume assessment.
Results: Mean platelet volume values decreased in patient groups in both active and remission phases than the control group (p-value< 0.001). There is an inverse correlation between platelets count and mean platelet volume (MPV) in group 1 during active phase and remission phase.
Conclusion: MPV can be used as a prognostic marker in patients with NS so it may be used to assess the clinical course and response to treatment.

Keywords: nephrotic syndrome; mean platelet volume; platelet count

1. Introduction

Nephrotic syndrome is one of the commonest kidney diseases in children. In which impairment of the glomerular function leads to leakage of protein into urine. This protein leakage is responsible for the main criteria of the disease which are hypoproteinemia, hypoalbuminemia, generalized edema and hyperlipidemia [1].

Patients with nephrotic syndrome are at increased risk for the development of thromboembolic complications. The increase of platelet count and activation may be important on hypercoagulopathy [2].

Mean platelet volume (MPV) can assess the size of the platelets in a blood sample. This index is used to determinate the rate of platelet production in patients who suffer from problems or diseases related to platelet destruction or bone marrow [3]. Low MPV may indicate chronic kidney disease and its association with a high platelet count may suggest an infection or inflammation [4].

In this study, we investigate the role of MPV as a prognostic biomarker in patients with nephrotic syndrome and its clinical importance in the follow up of this chronic disease.

Subjects and Methods

This prospective comparative study was done in the department of Pediatrics at Minia University Hospital, El-Minia, Egypt. The study was carried out over a period of 7 from August 2014 - 28th February 2015. An informed consent was obtained from parents after the nature and purpose of the study had been explained to them and were fully understood.

Ethical approval was obtained from the ethical committee of the faculty of medicine, Minia University. Eighty children were included in the study and divided into three groups

- Group 1: Steroid sensitive nephrotic syndrome (26 patients)
- Group 2: Steroid-resistant nephrotic syndrome (14 patients).
- Group 3: Forty healthy children (22 Male, 18 Female) were included in the study as a control group.

All enrolled patients in 1st and 2nd groups fulfilling the following criteria

- Age of onset of nephrotic syndrome less than 16 years.
- Steroid sensitive NS.
- Steroid-resistant NS.

We exclude from 1st and 2nd groups any patients with secondary NS, Congenital nephrosis., Inadequate data in the records., Patients dropping out during follow-up., Conditions associated with other inflammatory diseases that affect mean platelet volume as pneumonia bronchial asthma and peritonitis.

Detailed history taking including onset of disease, character of edema, type of nephrotic syndrome and the regimen of treatment obtained from all participating patients and thorough physical examination were done to all children including measurement of weight, height, arterial blood pressure, presence of edema and presence of any signs related to complications of nephrotic syndrome or treatment with steroids or cytotoxic drugs as hypertension, skin changes.

Laboratory investigations

Patients and controls were subjected to the followings:

i) **Blood sampling:** 3ml of venous blood was withdrawn from each subject divided into:
   - One ml of venous blood on tube containing EDTA for measuring Complete blood count including hemoglobin, platelet counts, mean platelet volume (MPV) by SYSMEX-KX-21N,JAPAN device. The range of expected values for MPV in our laboratory is 7 to 13 FL.
   - 2 ml of venous blood on a plain tube left to be clotted in the incubator and centrifuged, separated serum was used for measurement of AST, ALT, serum albumin, total cholesterol,urea and creatinine with spectrophotometric methods on Konelab 60i (made in Finland) device. Blood samples were withdrawn during active and remission phases of the disease.

ii) **Urine sample for simple urine analysis:** Fresh urine sample in a sterile wide container obtained in mid-stream urine after cleaning penile area in males or vulvar area in the female.

iii) **24Hour urine collection for measuring the amount of proteinuria in active and remission phases:** Method: collection of the sample within 24hour in clean wide neck container and keep the sample in refrigerator in 2-6℃ then by using sulphsalsalycilic acid reagent in a ratio3:1 (Turbimetry method) renal biopsy was previously performed for steroid-resistant nephrotic syndrome patients.

Statistical Methods

The collected data were coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 20. Descriptive statistics were done for numerical data by mean and standard deviation, while they were done for categorical data by number and percentage. The analysis was done for normally distributed quantitative variables using independent sample t-test to determine the statistical differences between the two groups.

The analysis was done for not normally distributed quantitative variables using Mann-Whitney U test to determine the difference between the two groups.

The analysis was done for normally distributed quantitative variables using One Way ANOVA test determine the statistical differences between more than two groups.

The analysis was done for not normally distributed quantitative variables using Kruskal-Wallis test to determine the difference between more than two groups.

Correlations were done using Pearson's Correlation for parametric data. The (r) ranged from (-1:+1). The degree of correlation determined according to the (r) (0-0.24 weak, 0.25-0.49 fair, 0.5-0.74 moderate, 0.75-1 strong).

The analysis was done for qualitative data using Chi-square test. The level of significance was taken at P value < 0.050 is significant.

Results

Eighty children (42 male and 38 female) were included in this study divided into 3 groups:

1. Group1: Corresponds to steroid sensitive nephrotic syndrome patients (SSNS) and those included 26 patients (18 miles (69.2%) and 8 females (30.8%)) with mean age 8.82 ± 3.46.
2. Group2: Corresponds to steroid-resistant nephrotic syndrome patients (SRNS) and those included 14 patients (2 males and 12 females) with mean age 8.32 ± 3.19.
3. Group3: Corresponds to control group and included 40 children (22 male and 18 female) with mean age 7.48 ± 2.62.

Comparison between patient groups (1, 2) and control group (group3) regarding Platelet parameters in table 1 shows a statistical significant increase in platelet count (×109/L) during active and remission phases in patient groups than the control group (P value 0.001, 0. 027 respectively) and also shows a statistical significant decrease in mean platelet volume (FL) during active and remission phases in patient groups than the control group (P value < 0.001, < 0.001 respectively).

Comparison between group1 and group2 as regards platelet parameters in active and remission phases in table 2 showing a significant increase in platelet count during the active phase in group 2 than group1 (P value 0.033) on the other hand, there were no statistically significant differences regarding platelet count in remission phase nor mean platelet volume in active and remission phases.

Study of platelet parameters in group1 steroid sensitive nephritic syndrome patients during active phase, remission phase and control group (group3) in table 3 showing statistically significant decrease in platelets count during remission phase than active phase but still higher than control group (P value <0.001) and statistically significant increase of mean platelet volume in remission phase than active phase but still lower than control group (P value <0.001).

Correlation between platelets count and mean platelet volume (MPV) in group 1 during active and remission phases in table 4 showing during active phase non-significant inverse fair correlation (r = -0.355, p = 0.075) and during remission phase shows significant inverse moderate correlation (r =-0.662,P = <0.001).

Correlation between platelets count and mean platelet volume (MPV) in group 2 in table 5 showing during active phase shows non-significant inverse weak correlation (r = -0.094, p = 0.750) and during remission phase shows non-significant inverse fair correlation (r =-0.272,P = <0.347).

Table 1: Comparison between patient groups (1, 2) and control group (group3) regarding platelet parameters in active and remission phases.

	Patients (G1,G2) (n=40)	Control (G3)(n=40)	P value
PLT count in active phase: ($\times 10^9$/L)Range Mean ± SD	(131-689) 365.7 ± 133.77	(162-426) 281.8 ± 72.03	0.001*
PLT count remission in phase: ($\times 10^9$/L) Range Mean ± SD	(111-645) 333.8 ± 126.34	(162-426) 281.8 ± 72.03	0.027*
MPV in active phase: (FL) Range Mean ± SD	(6.7-9) 8.04 ± 0.48	(9.1-10.8) 9.93 ± 0.62	< 0.001*
MPV in remission phase: (FL) Range Mean ± SD	(7.3-9.6) 8.75 ± 0.51	(9.1-10.8) 9.93 ± 0.62	< 0.001*

Table 2: Comparison between group1 steroid sensitive nephrotic syndrome patients (SSNS) and group2 steroid resistant nephrotic syndrome patients (SRNS) regarding platelet parameters in active and remission phases.

	Group I (SSNS) (n=26)	Group II (SRNS) (n=14)	P value
PLT count in active phase: ($\times 10^9$/L) Range Mean ± SD	(131-602) 334.88±125.52	(288-689) 422.92±134	0.033*
PLT count in remission phase: ($\times 10^9$/L) Range Mean ± SD	(111-537) 309.57±118.03	(248-645) 378.78±133.21	0.102
MPV active phase: (FL) Range Mean ± SD	(7.1-9) 7.98 ± 0.43	(6.7-9) 8.17 ± 0.57	0.565
MPV remission phase: (FL) Range Mean ± SD	(7.9-9.6) 8.77 ± 0.46	(7.3-9.5) 8.71 ± 0.62	0.943

Table 3: Comparison between platelet parameters of group1 steroid sensitive nephrotic syndrome patients during active phase, remission phase and control group (group3).

	Group 1 (SSNS)		Group III (Control) (n=40)	P value
	Active phase	Remission phase		
PLT ($\times 10^9$/L) Range Mean ± SD	(131-602) 334.88±125.52	(111-537) 309.57±118.03	(162-426) 281.8±72.03	<0.001*
MPV (/ FL) Range Mean ± SD	(7.1-9) 7.98 ± 0.43	(7.9-9.6) 8.77 ± 0.46	(9.1-10.8) 9.93 ± 0.62	<0.001*

Table 4: Correlation between platelets count and mean platelet volume (MPV) in group 1 steroid sensitive nephrotic syndrome patients during active and remission phases.

Group1 SSNS (n:26)	MPV			
	Active phase		Remission phase	
	r	P	r	P
PLT count	-0.355	0.075	-0.662	<0.001*

Table 5: Correlation between platelets count and mean platelet volume (MPV) in group 2 steroid resistant nephrotic syndrome patients during active and remission phases.

Group2 SRNS (n:14)	MPV			
	Active phase		Remission phase	
	r	P	R	P
PLT count	-0.094	0.750	-0.272	0.347

Discussion

Nephrotic syndrome (NS) is a clinical constellation of a group of symptoms and signs that may point to kidney [5], Thromboembolism is one of the most serious complications of nephrotic syndrome (NS) [6]. The pathophysiology of thrombogenesis in NS is not clear. The platelet count is almost universally elevated in NS [7]. The thromboembolic complications in the nephrotic syndrome can be attributed to the interplay of three components: endothelial cell injury, platelet hyperaggregability and hypercoagulability. In NS there is platelets activation with platelet hyperaggregation and hyperactivity [8]. MPV may be an indirect indicator of platelet activation [9].

In the present study as regarding Platelet parameters we found statistically significant increase in platelets count during active and remission phases in patient groups than control group (P value 0.001, 0.027 respectively) and also shows significant decrease in mean platelet volume during active and remission phases in patient groups than control group (P value < 0.001, < 0.001 respectively).Our results in agreement with the results of Kaan Gulleroglu *et al*., 2014 [10] and Ismail *et al*., 2013 [11]. Thrombocytosis can be a result from hypovolemia, hypo albuminuria, and hemoconcentration and increased platelet activity are associated with platelet volume [10]. Thrombocytosis is very serious in patients with nephrotic syndrome because it may result in the development of thromboembolism. Two to five percent of children with NS develop thromboembolism. The risk seems higher in children with steroid resistant compared with steroid sensitive disease [12].

The study of Park & Shin, 2011 [13] found that thrombocytosis is contributing factor for development of thromboembolism and there were other factors involved in this complication as activation of the coagulation system, loss of coagulation inhibitors such as antithrombin III in the urine, changes in the glomerular hemostatic system, intravascular volume depletion and exposure to corticosteroids and diuretics.

In comparison between group1 and group2 regarding platelets parameter (table 6) shows a significant increase in platelets count during active phase in group 2 than group1 (P value 0.033).

Our results in coordinance with results of Gipson *et al*., 2009 [12]. Who studied management of childhood-onset nephrotic syndrome and his results suggest that incidence of thrombocytosis and thromboembolism is higher in steroid resistant nephrotic syndrome patients than steroid-sensitive patients.

Also our results in agreement with results of Kaan Gulleroglu *et al*., 2014 [10] who explained that by severe and long-standing hypovolemia and hypoalbuminemia occurs in steroid resistant nephrotic syndrome patients.

In comparison between platelet parameters in group1 steroid sensitive nephrotic syndrome patients during active phase, remission phase and control group shows significant decrease in platelets count during remission phase than active phase but still higher than control group (P value <0.001) and significant increase of mean platelet volume in remission phase than active phase but still lower than control group (P value<0.001).

Our results showed also the same finding in the comparison between platelet parameters in group2 steroid-resistant nephrotic syndrome patients during active phase, remission phase, and control group nbvn. Our results in co-ordinance with the results of *Kaan Gulleroglu et al.*, 2014 [10] who studied the clinical importance of MPV in children with nephrotic syndrome and concluded that MPV could be a marker for nephrotic syndrome as its value decrease with the beginning of relapse and begin to increase with remission and MPV value in diseased children either in remission or relapse phases still lower than normal children so we could make follow-up to these patients by MPV value and we could detect the response of treatment.

In contrast to us, the study of Ismail., 2013 [11] who studied the role of platelet activation in determining response to therapy in patients with the primary nephrotic syndrome and his study include steroid-sensitive patients in partial and complete remission and steroid resistant nephrotic syndrome patients. This study found a significant decrease in MPV levels after treatment comparing with first admission levels and control group so MPV could be used as a marker to predict response to treatment.

Our results could be explained by the fact that Mean platelet volume (MPV) is a reflection of platelet size, which correlates with platelet function and activation [14].

Increased platelet activity is associated with platelet volume. Large platelets that contain more dense granules are metabolically and enzymatically more active than small platelets and have higher thrombotic potential. MPV, a determinant of platelet activation is a newly emerging risk factor for atherothrombosis so understanding the role of platelets in a variety of thrombotic and inflammatory disorders has substantially improved owing to the recent advances in the quantification of laboratory markers of platelet function. MPV has emerged as a relatively reliable marker of thrombopoiesis and platelet function [15].

As regards the correlation between platelets count and mean platelet volume (MPV) in group 1 during active phase shows inverse fair correlation ($r = -0.355$, $p = 0.075$) and during remission phase shows significant inverse moderate correlation ($r = -0.662$, $P = <0.001$).

Similarly, the study of Guida *et al*., 2003 [16] who reported that Platelet count had an inverse relationship with MPV because young platelets are larger than older ones, and the authors evaluated the use of MPV in the differential diagnosis of hyper-destructive and hyperproductive types of thrombocytopenia.

Also, sola-visner *et al*., 2007 [17] stated that in several conditions increased platelet count was associated with a decrease in MPV values such as inflammatory bowel disease and rheumatoid arthritis or an increase in MPV may accompany a lower platelet count such as hyperthyroidism.

An important limitation of our study is the small number of the patients.

Conclusion

Our results suggest that MPV values predict the prognosis of patients with NS by reflecting increased inflammatory response and platelet activation. Therefore, it may also, be helpful in follow up of the patients and can predict responsiveness to the treatment.

We recommend that*:*

- Routine use of Mean platelet volume in nephrotic syndrome patients as it is an easy, available and simple method to determine the prognosis of the disease and response to treatment*.*
- A careful follow-up is important, especially for development of SRNS, in patients with low MPV accompanied by thrombocytosis*.*
- Future studies with large sample size to study the possible effect of drugs used for the treatment on the MPV value.

What this study adds to existing knowledge

We can use MPV values accompanied by platelets count to predict response to treatment and can also early predict the risk of thromboembolism. Our findings that that the changes in platelets parameters decrease in the remission indicate that these changes are reversible and their values even in the remission still different from control group indicate that the body remain in a state of low grade inflammation even in remission and also carrying a risk of thromboembolism.

Conflict of interest

We declare no conflict of interest.

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Authors' contributions

ANM participated in the study design, data collection, analysis and manuscript writing. GBM participated in manuscript writing. MGH participate in data collection, analysis. HMK did the lab. Work. All authors read and approved the final manuscript*.*

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