ISSN : 2350-0743

www.ijramr.com

International Journal of Recent Advances in Multidisciplinary Research
Vol. 06, Issue 01, pp.4369-4372, January, 2019

RESEARCH ARTICLE

RED CELL DISTRIBUTION WIDTH AND MEAN PLATELET VOLUME AS AN INFLAMMATORY MARKER İN MULTIPLE SCLEROSIS

***Sule Aydin Turkoglu, Tarik Eroglu, Elif Sultan Bolac, Muhammed Nur Ogun and Serpil Yildiz, NebilYildiz**

Department of Neurology, AbantIzzetBaysal University Medical Faculty, Bolu, Turkey

ARTICLEINFO

Article History:
Received 25th October, 2018
Received in revised form
18th November, 2018
Accepted 20th December, 2018
Published online 30th January, 2019

Keywords:
Multiple Sclerosis,
Inflammation, RDW-MPV

ABSTRACT

Introduction: We aimed to investigate the possible association between MS and hemogram parameters (RDW and MPV and neutrophil to lymphocyte ratio). **Methods:** We retrospectively analyzed the files of MS patients. Hemogram parameters were evaluated between attack and remission period and with control subjects. For each group, leukocyte count (WBC), neutrophil count (neu), lymphocyte count (lym), Hemoglobin (Hb), Hematocrit (Htc), mean corpuscular volume (MCV), red cell distribution width (RDW), platelet count (PLT) and mean platelet volume (MPV) levels were recorded. Statistical analysis was performed. **Results:** 48 MS patients' age and gender were not significantly different from 51 control subjects. There was no statistically significant difference between study and control groups in terms of WBC, neutrophil count, lymphocyte count, neutrophil to lymphocyte ratio, Hb, Htc, MCV and platelet count (all $p>0.05$). RDW was significantly increased in MS patients within attack period. MPV was also significantly increased in patients with MS compared to control subjects. We showed that only RDW was significantly decreased, others not changed, in study group in remission period compared to attack period ($p<0.001$). **Discussion and Conclusion:** This is the first report in literature that pointed an association between MS and hemogram parameters; RDW and MPV. We initially showed that, increase in both MPV and RDW may suggest the relationship with inflammatuary response in MS patients' attack period. Secondly, RDW should be a good marker of treatment follow up for MS patients due to substantial decrease in remission period. Prospective studies with larger cohort are needed for the sake of more meaningful suggestions.

INTRODUCTION

Multiple sclerosis (MS) is a neurological disease characterized with inflammation (Calabresi, 2004; Lassmann, 2007). The myelinated axons in central nervous system are affected in varying degrees in the course of MS (Lassmann, 2007; Weinshenker, 1996). Although the etiology is unclear, it is widely accepted that genetic predisposition and triggering factor(s) combined are responsible of autoimmune attacks in central nervous system (Goldenberg, 2012). Inflammation may play a crucial role in the pathogenesis of MS. It has been shown that, tumor necrosis factor (TNF) was increased in serum and cerebrospinal fluid of the subjects with MS (Lassmann, 2007; Sharief, 1991). Moreover, it is reported that, TNF targeted anti-inflammatory therapy with anti-TNF agents prevent disease progression (Williams *et al*., 2018). The studies in recent years revealed that, platelets play crucial role not only in homeostasis but also in inflammation (Thomas, 2017). Association between platelets and inflammatory reactions has been described in a number of conditions (Jenne, 2015). Mean platelet volume (MPV) is accepted as a marker of platelet activation.

Corresponding author: **Sule Aydin Turkoglu,**
Department of Neurology, AbantIzzet Baysal University Medical Faculty, Bolu, Turkey.

It has been reported in literature that MPV was related with the diseases characterized with inflammation (Ataç, 2018; Aktas *et al*., 2018). Another simple hemogram parameter likewise MPV is red cell distribution width (RDW), which is a measure of the size variability of erythrocytes. Despite it increases in iron deficiency anemia, it has also been speculated that it should be associated with inflammatory conditions (Duman *et al*., 2018; Karagoz *et al*., 2017; Sarman *et al*., 2017). Another inflammatory measure derived from routine hemogram test was neutrophil to lymphocyte ratio (N/L ratio). N/L ratio supposed to be associated with inflammation recently (Imtiaz *et al*., 2012) because, a number of studies revealed it's prognostic value in different diseases characterized with overt or subclinical inflammation (Eroglu *et al*., 2017). To our knowledge, there are no reports in literature about MPV and RDW values and N/L ratio of MS patients. Therefore, in this retrospective study, we aimed to investigate the possible association between MS and hemogram parameters (RDW and MPV and N/L ratio).

MATERIALS AND METHODS

The study has been conducted in accordance with the principles of the Helsinki Declaration and approved by the

local Institutional Review Board (2014/27-86). Our study group was consisted of patients with MS. The diagnosis of MS was based on the criteria of Mc Donald's. Healthy subjects who visited the clinics of our institution for check up were enrolled in the study as control group. The data obtained from study and control groups from computerized database of our hospital. Exclusion criteria were as follows: anemia (especially iron deficiency), diabetes mellitus, and other chronic inflammatory disease, medications that may affect hemogram results (e.g. aspirin). We retrospectively analyzed the files of patients. Hemogram parameters in blood samples which were taken when the patients applied to our clinic due to attack period but prior to attack treatment were evaluated. Blood samples at attack period are defined as blood samples which obtained prior to attack therapy in patients presented with acute attack within 1 week of the symptoms beginning. Hemogram parameters of the same patients were also evaluated which were taken in the remissions period, at least 2 months after the attack period. The obtained data were compared with hemogram parameters of age and sex matched healthy control group.

Also hemogram parameters between attack and remission period were compared. Patients' characteristics and laboratory data; leukocyte count (WBC), neutrophil count (neu), lymphocyte count (lym), Hemoglobin (Hb), Hematocrit (Htc), mean corpuscular volume (MCV), RDW, platelet count (PLT) and MPV levels of the study cohort were recorded. Statistical analyses were performed by SPSS software (SPSS 15.0 for Windows, Chicago, IL, USA). Variables that distribute homogenously expressed as mean +/-SD and compared between study groups by independent samples t test. Variables that distribute non-homogenously expressed as median (min-max) and compared between study groups by Mann-Whitney U test. P value <0.05 was considered as statistically significant.

RESULTS

Forty-eight patients with MS and 51 healthy subjects enrolled to the study. Median age of the study group (39 (19-59) years) was not significantly different from control group (39 (19-61 years)) (p=0.08).

Table 1.General characteristics and laboratory data of the study in MS relapse and control group

		Group		
		Relapse of Study	Control	P
Gender	Men (n)	19	16	0.39
	Women (n)	29	35	
		Mean ± Standard Deviation		
WBC (u/mm^3)		7.32 ± 2.09	7.03±1.37	0.41
Lym (u/mm^3)		2.02±0.67	2.13 ± 0.5	0.36
Hb (g/dl)		13.4 ±1.8	13.9±1.4	0.11
Htc (%)		40.1±4.5	40.8 ±3.9	0.35
MCV (fL)		86±5	86±4	0.45
		Median (Min - Max.)		
Age (years)		39 (19-59)	35 (19-61)	0.08
Neu (u/mm^3)		4.3 (1.5-12)	4.3 (1.7-7.4)	0.42
Neu/lymratio		2.1 (0.8-10.2)	2 (0.8-5.6)	0.18
RDW (%)		16.2 (13.7-19.8)	13.7 (10.6-16.6)	<0.001
PLT (u/mm^3)		271 (166-1000)	257 (158-446)	0.78
MPV (fL)		8.7 (6.3-10.8)	7.9 (5,8-11.6)	0.007

Table 2. Laboratory parameters of MS patients in relapse and remission periods

Laboratory Parameter	Period		P
	Relapse	Remission	
	Mean ± Standard Deviation		
WBC (u/mm^3)	7 ± 2.1	6.8 ±1.7	0.07
Neu (u/mm^3)	4.5 ±1.8	4.2 ±1.4	0.25
Lym (u/mm^3)	2±0.6	1.9 ±0.7	0.09
Neu/lymratio	2.6 ±1.6	2.6±1.5	0.80
Hb (g/dl)	13.4 ±1.8	13.6 ±1.5	0.19
Htc (%)	40.1±4.5	40.7 ±4.1	0.14
MCV (fL)	85 ±5	85 ±4.5	0.47
RDW (%)	16.2 ±1.08	13.6±1.5	<0.001
PLT (u/mm^3)	271 ±119	285 ±87	0.21
MPV (fL)	8.7 ±1.3	8.9 ±1	0.19

Table3.Comparison of laboratory data of the MS patients in remission period and control group

	Group		
	Remission of Study	Control	P
	Mean ± Standard Deviation		
WBC (u/mm^3)	6.8 ± 1.7	7.03±1.37	0.47
Lym (u/mm^3)	1.86±0.71	2.13 ± 0.5	0.03
Hb (g/dl)	13.7 ±1.6	13.9±1.4	0.47
Htc (%)	40.7±4.1	40.8 ±3.9	0.87
MCV (fL)	85±5	86±4	0.06
	Median (Min - Max.)		
Neu (u/mm^3)	4.2 (2.2-9.2)	4.3 (1.7-7.4)	0.99
Neu/lymratio	2.6 (0.8-8.3)	2 (0.8-5.6)	0.07
RDW (%)	13.6 (10.7-17)	13.7 (10.6-16.6)	0.57
PLT (u/mm^3)	286 (143-621)	257 (158-446)	0.17
MPV (fL)	9 (7-11)	7.9 (5,8-11.6)	<0.001

Gender was not significantly different between groups (p=0.39). There were 19 men and 29 women in study group and 16 men and 35 women in control group. There was no statistically significant difference between study and control groups in terms of WBC, neutrophil count, lymphocyte count, neutrophil to lymphocyte ratio, Hb, Htc, MCV and platelet count (all p>0.05). RDW was significantly increased in patients with MS (16.2 (13.7-19.8)) compared to control subjects (13.7 (10.6-16.6)) (p<0.001). MPV was also significantly increased in patients with MS (8.7 (6.3-10.8)) compared to control subjects (7.9 (5,8-11.6)) (p=0.007). General characteristics and laboratory data of the study within attack period and control group were given in table 1. In further analyses of the laboratory data of MS patients, we showed that only RDW was significantly decreased, others not changed, in study group in remission period compared to attack period (p<0.001). The changes in laboratory parameters in MS patients between attack and remission periods were summarized in table 2. Table 3 shows Comparison of laboratory data of the MS patients in remission period and control group.

DISCUSSION

In present study, we initially showed that, increase in both MPV and RDW may suggest the diagnosis of MS patients' attack period. Secondly, RDW may be a good marker of treatment follow up for MS patients due to substantial decrease in remission period however this finding should be supported with future studies. Literature is full of data about the association between MS and inflammation (Dendrou, 2015; Haider, 2015). Bitsch *et al* reported that axonal damage in MS was mediated with inflammatory cells such as T lymphocytes and macrophages (Bitsch *et al*., 2000). Another evident for inflammatory basis of the MS should be that matrix metalloproteinases act as modulator of inflammation and cause invasion of neural tissue by immune system in patients with MS (Haider, 2015; Leppert, 2001). This is the first report in literature that pointed out an association between MS and hemogram parameters; RDW and MPV. What is the underlying mechanism of RDW increase in MS? As mentioned before, MS is considered as an auto-inflammatory disease. Long term inflammation may interact with iron storage and utilization in erythropoiesis in bone marrow. Cooper *et al* showed that TNF alpha and interferon gamma may diminish erythroid precursors in bone marrow (Cooper *et al*., 2003). Moreover, it has been reported that inflammatory molecules may modify erythropoiesis (Means, 1992; Dai, 1998). Larger and smaller erythrocytes produced by bone marrow may cause the heterogeneity in red blood cell size and thus, elevation in RDW.

What is the reason or reasons of MPV increase in MS? Because of inflammatory base of the disease, we shall focus on the effects of inflammation on bone marrow. Megakaryocytes stimulated by inflammatory cytokines may produce larger platelets which cause an elevation in MPV value. Another possibility should be that inflammatory molecules activate the platelets in bloodstream which may increase the dimension of the platelets. RDW of the MS patients significantly decrease in remission period compared to attack period, suggesting that RDW could be used as a predictor of disease activity. However, MPV was not significantly different between attack and remission periods. It's clear that we expected a reduction in MPV earlier than a reduction in RDW, because of the shorter life span of platelets compared to erythrocytes. Maybe, we shall speculate that, erythroid precursors are more sensitive to the inflammatory markers than megakaryocytes. MPV was significantly elevated but, RDW was not different in MS patients during remission compared to controls. We shall speculate that subclinical inflammation in remission period could be adequate to cause an elevation in MPV but not in RDW due to relatively shorter lifespan of thrombocytes compared to erythrocytes. Two major limitations of present study are small study population and retrospective design, which make our results cautious. However, this retrospective study may stimulate future prospective studies in this area. In conclusion, MPV and RDW may be helpful in the diagnosis of MS and RDW may also be useful in evaluation of the treatment response. However, prospective studies with larger cohort are needed for the sake of more precious suggestions.

REFERENCES

Aktas G., Kocak MZ., Duman TT., Erkus E., Atak BM., Sit M., *et al*., Mean Platelet Volume (MPV) as an inflammatory marker in type 2 diabetes mellitus and obesity. Women (n).30:35.

Ataç H., Canpolat F., Eskioglu F. 2018. Evaluation of Mean Platelet Volume in Patients With Behcet's Disease as an Indicator of Vascular Thrombosis. Archives of Iranian Medicine (AIM). 21(6).

Bitsch A., Schuchardt J., Bunkowski S., Kuhlmann T., Brück W. 2000. Acute axonal injury in multiple sclerosis: correlation with demyelination and inflammation. *Brain.,* 123(6):1174-83.

Calabresi PA. 2004. Diagnosis and management of multiple sclerosis. *American family physician*.70(10):1935-44.

Cooper AC., Mikhail A., Lethbridge MW., Kemeny DM., Macdougall IC. 2003. Increased expression of erythropoiesis inhibiting cytokines (IFN-γ, TNF-α, IL-10, and IL-13) by T cells in patients exhibiting a poor response to erythropoietin therapy. *Journal of the American Society of Nephrology.,* 14(7):1776-84.

Dai CH., Price JO., Brunner T., Krantz SB. 1998. Fas ligand is present in human erythroid colony-forming cells and interacts with Fas induced by interferon γ to produce erythroid cell apoptosis. *Blood*., 91(4):1235-42.

Dendrou CA., Fugger L., Friese MA. 2015. Immunopathology of multiple sclerosis. *Nature Reviews Immunology.* 15(9):545.

Duman TT., Aktas G., Atak B., Kocak MZ. 2018. Is Mean Platelet Volume to Platelet ratio a promising indicator of diabetic regulation in type 2 diabetes mellitus? JMR. 2018;4(3):137-9.

Eroglu T., Turkoglu SA., Bolac ES., Yildiz S., Yildiz N. 2017. Hemogram parameters in epilepsy may be indicators of chronic inflammation and hypoxemia. *Journal of Neurology and Clinical Neuroscience.,* 1(1).

Goldenberg MM. 2012. Multiple sclerosis review. *Pharmacy and Therapeutics*., 37(3):175.

Haider L. 2015. Inflammation, iron, energy failure, and oxidative stress in the pathogenesis of multiple sclerosis. Oxidative medicine and cellular longevity.2015.

Imtiaz F., Shafique K., Mirza SS., Ayoob Z., Vart P., Rao S. 2012. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. *International archives of medicine.,* 5(1):2.

Jenne CN., Kubes P. 2015. Platelets in inflammation and infection. Platelets. 26(4):286-92.

Karagoz I., Aktas G., Yoldas H., Yildiz I., Ogun MN., Bilgi M. *et al*., 2017. Association between hemogram parameters and survival of critically ill patients. *Journal of intensive care medicine.* 0885066617703348.

Lassmann H., Brück W., Lucchinetti CF. 2007. The immunopathology of multiple sclerosis: an overview. *Brain pathology.,* 17(2):210-8.

Leppert D., Lindberg RL., Kappos L., Leib SL. 2001. Matrix metalloproteinases: multifunctional effectors of inflammation in multiple sclerosis and bacterial meningitis. *Brain research reviews.* 36(2):249-57.

Means RJ., Krantz SB. 1992. Progress in understanding the pathogenesis of the anemia of chronic disease [see comments]. *Blood.,* 80(7):1639-47.

Sarman H., Isik C., Boz M., Boyraz I., Koc B., Turkoglu SA. 2017. Is the red cell distribution width a predictive parameter in patients with cubital tunnel syndrome requiring surgery? *Acta Ortopédica Brasileira*., 24(4).

Sharief MK., Hentges R. 1991. Association between tumor necrosis factor-α and disease progression in patients with multiple sclerosis. *New England Journal of Medicine*. 1991;325(7):467-72.

Thomas MR., Storey RF. 2015. The role of platelets in inflammation. Thrombosis and haemostasis. 114(03):449-58.

Weinshenker BG. 1996. Epidemiology of multiple sclerosis. *Neurologic clinics*.14(2):291-308.

Williams SK., Fairless R., Maier O., Liermann PC., Pichi K., Fischer R. *et al*. 2018. Anti-TNFR1 targeting in humanized mice ameliorates disease in a model of multiple sclerosis. Scientific reports., 8(1):13628.

****