Original Article 10.30477/cjm.2022.309153.1024

Evaluation of Red Cell Distribution Width Alterations with Severity of Migraine

Rokhsareh Meamar[1], Salimeh Janghorban[2], Behnaz Ansari[2], Anahita Saeedi[3], Amiromayoun Atefi[4], Farzaneh Tavakoli[5]

1. Isfahan clinical toxicology research center, Isfahan university of medical sciences, Isfahan, Iran.
2. Clinical research development center, Najafabad branch, Islamic Azad University, Najafabad, Iran.
3. Department of Biostatistics, School of Public Health & Health Sciences, University of Massachusetts, Amherst, MA, USA.
4. Student research academy, school of medicine, Guilan University of medical sciences, Rasht, Iran.
5. Hematopoietic Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

ABSTRACT

Introduction: Migraine is an inflammatory condition with high prevalence. Approximately 18% of women and 6% of men suffer from Migraine. It is classified into two groups based on aura manifestations. Aura is characterized by any combination of visual, hemisensory, or language abnormalities. Although not completely elucidated, one possible explanation for its cause may be related to the reduction of blood flow of the brain's arteries or increased hemoglobin level. In this study, we aim to find out the relationship between migraine and red cell distribution width (RDW). **Methods**: 100 patients with migraine who were referred to specialized clinics Al-Zahra hospital between 2015-2016 and age and sex-matched 100 control subjects enrolled in this study. The disease diagnosis was confirmed by a neurologist. Fasting venous blood samples were taken from subjects for performing CBC, ferritin and, iron, and TIBC tests. HIT6 questionnaire was considered to assess the severity of migraines. **Results**: There were 100 patients with a median age of 36 years (range 18-50). 22% were male and 78% were female. Data analysis didn't show any relationship between migraine severity and RDW. Also, RDW didn't have any relationship with the type of migraine (with aura or without aura). **Conclusion**: This study could not reveal any significant association between RDW and migraine. Observing high RDW in both case and control groups brings us to the hypothesis high prevalence of iron deficiency in our country. According to the results, low ferritin levels had a relationship with increased severity of migraine.

Keywords: Migraine Disorders, Aura, Erythrocyte Indices, Anemia

Recived Date: 05 October 2021
Revised Date: 03 March 2021
Accept Date: 13 March 2022
Published Date: 24 May 2022
Editor: M. Pourfridoni (Conflict of interest: None)
Reviewers: M. Khosravi (Conflict of interest: None), M. Honarvar (Conflict of Intrests: None)

*Correspondence to: Farzaneh Tavakoli Hematopoietic Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Tehran, IranIran National Elite Foundation, Tehran, 93111-14578, Iran.
Email address: farzanehtavakoli1990@yahoo.com
ORCID: 0000-0002-5898-591X

Cite as : Rokhsareh Meamar, Salimeh Janghorban, Behnaz Ansari, Anahita Saeedi, Amiromayoun Atefi, And Farzaneh Tavakoli. Evaluating Evaluation of Red Cell Distribution Width Alterations with Severity of Migraine. Canon Journal of Medicine.2022 March; 3(1):15-18

INTRODUCTION

Migraine is the third most common and the seventh most disabling disease worldwide (1). Numerous studies have demonstrated a relationship between migraine and inflammation and also, inflammatory factors of the immune system (2-4). Thirty percent of patients with migraines experience focal neurologic symptoms called auras before the attacks and it has been suggested that inflammatory cytokines are released in this phase (5, 6). In addition, neurogenic inflammation is involved in the pathogenesis of migraine (7).

Red cell distribution width (RDW), an indicator of anisocytosis, is typically evaluated in the complete blood count test (8). This parameter can be considered as an inflammatory marker, and its role in many diseases including leukemia, Alzheimer's disease, kidney disease, and some autoimmune illnesses have been previously discussed (9-13). RDW can be altered by various pathological conditions, including a delay in erythrocyte clearance that increases anisocytosis (14). In a study of HIV patients, it was found that there is a positive relationship between RDW and systemic inflammatory biomarkers including C-reactive protein, tumor necrosis factor alfa (TNF-a), interleukin 6 (IL-6), and IL-8 (15). High RDW can be one of the symptoms of erythropoiesis disorders and hyper erythrocytosis can cause hyperviscosity, one of the factors of migraine pathogenesis (16, 17). Indeed, the relationship between migraine and iron metabolism in some studies has been discussed (18-20).

Since a limited number of studies have evaluated the effect of RDW on migraine, the current study was conducted to measure the relationship between this hematologic parameter and this debilitating disease.

MATERIAL AND METHODS

Patients

All patients referred to the headache clinic of the Alzahra hospital from April 2014 to March 2016 were included in the initial analysis. The diagnosis of migraine was confirmed by a neurologist according to the International Classification of Headache Disorders-II diagnostic criteria (21). 70 patients had migraine

with aura and 30 patients without aura. The HIT6 questionnaire was used to assess the severity of headaches (22). Exclusion criteria were considered as age younger than 18 or older than 50, body mass index lower than 18 or higher than 30, smoking, corticosteroid therapy, contraceptives intake, pregnancy, breastfeeding women, any comorbidities including cardiovascular patients, history of hypertension, hypercholesterolemia malignancy, renal liver failure, hematological disorders, and autoimmunity. Considering these criteria, finally, 100 migraine patients and age- and sex-matched 102 control healthy individuals who had no headache of any kind. were enrolled in the study All patients were given the consent form after they were informed about the procedures and the aim of the investigation.

Blood assay

Fasting blood was collected in clot tubes for ferritin testing and EDTA tubes for RDW measurement. Serum ferritin was analyzed using a simple chemiluminescence method (Elecsys®, Roche Diagnostics, Mannheim, Germany). RDW measurements were conducted using a hematology analyzer (Sysmex K1000, Sysmex Corp., Kobe, Japan).

Statistical analysis

The patients' characteristics were demonstrated as frequency (%) or mean± standard deviation. Hemoglobin (Hb), iron (Fe), total iron-binding capacity (TIBC), and ferritin along with RDW were all included in the study as risk factors for determining a relationship with the severity of migraine headaches. The normality of the data set was evaluated through the Kolmogorov-Smirnov test and the homogeneity of the variances of the two groups of migraine with and without aura was determined. Then the independent T-test and ANOVA were employed to compare the differences among variables. A Pearson correlation was applied for determining a relationship between these risk factors and the severity of the migraine. The univariable and multivariable regression analyses were used to identify the predictors of migraine. The relationship between the levels of RDW, Hb, Fe, TIBC, and ferritin in patients, was carried out using the Pearson correlation as well.

RESULTS

The blood sample of 70 patients who had migraine with aura and 30 patients who had migraine without aura were analyzed. The results of the statistical analysis indicated that the differences in the type of migraine with or without aura were not significant in men and women. Gender didn't demonstrate any significant effect on both groups of case and control (Table1).

The severity of the disease in cases with and without aura was 62.9± 6.99 and 67.2 ± 6.23, respectively. The independent T-test revealed that the mean severity was statistically significant in two groups of patients (P-value: 0.005). The disease severity in men and women with migraine were 57.8±1.78 and 66± 0.61, respectively. The mean severity in women was greater than men (P-value: 0.000).

To determine the relationship between RDW level and the severity of the attacks, the Pearson correlation was applied. The results indicated that the severity of the disease is associated with an increase in RDW and TIBC (P-value< 0.05). Additionally, the increase in the disease severity is significantly associated with a decrease in Hb and Ferritin (P-value< 0.05) (Table 2).

Table 1. The characteristics of the cases with migraine and the control group

Sex N(%)					
Migraine with aura		Migraine without aura		Control	
Men	Women	Men	Women	Men	Women
26(86.7)	4(13.3)	70(70%)	52(74.3)	73(71.3)	29(28.4)

Table 2. The severity of the disease

	With aura	Without aura	p-value	Men with migraine	women with migraine	p-value
Average HIT-6 Sum Scores	62.9 ± 6.99	67.2 ± 6.23	0.005	57.8± 1.78	66± 0.61	0.000

Table 3. Correlation of RDW with severity of the attacks

	Correlation	P-value
Hb	0.213-	0.033
RDW	0.139	0.167
Fe	-0.184	0.068
TIBC	0.085	0.404
ferritin	-0.332	0.001

An increase in RDW was significantly associated with a decrease in ferritin and Hb (P-value< 0.05). In the control group, the results showed that an increase in RDW was significantly associated with a decrease in ferritin, Hb, and Fe (P-value< 0.05). The results of the Pearson correlation test among the risk factors revealed that the mean between Hb and RDW, Hb and TIBC, RDW and Fe, and TIBC, ferritin and RDW, ferritin and TIBC have an inverse relationship whereas the mean between ferritin and Fe have a positive relationship.

The analysis of variance test (ANOVA) was assessed for the RDW mean and the repeating attacks of the disease in one month, which was not statistically significant (P-value> 0.05).

An independent T-test was employed for comparing the risk factors. TIBC and ferritin in both groups of migraine with and without aura were significant (P-value< 0.05) (Table 3). Besides, the T-test was performed for comparing groups of case and control, however, the difference was not significant for none of the risk factors (Table 4).

Based on the regression model, RDW cannot predict the severity of migraine. Ferritin is the only risk factor that is significantly associated with the severity of migraine attacks (P-value< 0.05) (Table 3).

DISCUSSION

High RDW is an inflammatory condition and the erythropoiesis and iron status affect its level. Migraine, on the other hand, is considered to be an inflammatory disease that has been studied in association with iron and red blood cells in some previous literature. Being inexpensive and easy to measure were other reasons that we focused on the association between RDW

Table 4. The comparison of RDW mean in patients with and without migraine and The comparison of RDW mean in case and control group (Hb: Hemoglobin; RDW: Red blood cell distribution width ; TIBC: Total iron binding capacity)

	Mean± SD			Mean± SD		
	Migraine without Aura	Migraine with Aura	P value	Control	Case	P value
Hb	13.2 ±0.16	12.8 ± 0.29	0.189	13.1 ± 0.14	13.4 ± 0.16	0.168
RDW	13.4 ± 0.14	15.1 ± 1.04	0.116	13.9 ± 0.33	13.5 ± 0.23	0.312
Fe	71.8 ± 4.12	65.8 ± 4.76	0.342	70.1 ± 3.23	78.6 ± 3.51	0.074
TIBC	319.8 ± 6.97	363.7 ± 10.7	0.001	333.1 ± 6.16	322.4 ± 8.95	0.326
Ferritin	54.9 ± 5.02	35.4 ± 5.08	0.021	49 ± 3.91	57 ± 8.95	0.343

and migraine.

In our cross-sectional study, there was no significant relationship between migraine and RDW, in comparison with the control group. Also, subgroup analysis did not show any significant differences in RDW among patients with and without aura. Another result of our study, which can be considered valuable, is the significant association between decreased ferritin and hemoglobin levels with increased severity of the attacks. The results of the study conducted by Celikbilek (23), which was most similar to our study, indicated that there is a significant relationship between the level of this factor in migraine patients compared to the control group.

The Association between the high level of hemoglobin and migraine has been discussed in several studies with contradicting results. It has been reported that high Hb is associated with migraine in men livening at high altitudes (24) and in patients with congenital heart disease (25). On the other hand, in a cross-sectional study, no significant differences were found between Hb and disease in patients without aura (26). In the Celikbilek study, no significant relationship was found when the data were analyzed by gender, due to a large number of women among the patients present in the study (23). In addition, there are some reports on controlling hemoglobin levels in people with hemochromatosis which can improve the symptoms of migraine (27, 28).

Some studies are in line with our results. A 2013 Investigation by Pamuk et al. among people with iron deficiency anemia has shown a high frequency of migraines. The interesting finding was the lower hemoglobin level in migraine patients with aura. It should be noted that since there was no control group, one should be cautious in interpreting the results of their study (18). These results were confirmed by a pediatric study on the frequency of restless leg syndrome in migraine patients compared to the control group since one of the causes of this syndrome is iron deficiency (29). A 2016 study about migraine and frequency of comorbidities, revealed a higher rate of iron deficiency anemia (30). Another finding that may confirm our results was among women with end-menstrual migraine. The report acknowledges that migraine is related to blood loss rather than to hormone levels. Remarkably, ferritin levels were low in these patients and they responded favorably to iron supplementation (31).

CONCLUSION

All things considered, we contend that both iron overload and iron deficiency are associated with worsening migraines. Therefore, balancing iron metabolism and controlling it at normal levels may be effective in improving migraine patients. However, further investigations, especially on the mechanism of both conditions as well as systematic reviews on this field, can lead us to more accurate results.

ETHICAL CONSIDERATION

This study was registered is approved by the institutional review board and patients fillid in the consent.

CONFLICT OF INTRESETS

There are no conflicts of interest in terms of the present manuscript.

REFRENCES

1. Lukacs M, Tajti J, Fulop F, Toldi J, Edvinsson L, Vecsei L. Migraine, neurogenic inflammation, drug development-pharmacochemical aspects. Current medicinal chemistry. 2017;24(33):3649-65.
2. Conti P, D'Ovidio C, Conti C, Gallenga CE, Lauritano D, Caraffa A, et al. Progression in migraine: role of mast cells and pro-inflammatory and anti-inflammatory cytokines. European journal of pharmacology. 2018.
3. Yücel M, Kotan D, Gurol Çiftçi G, Çiftçi I, Cikriklar H. Serum levels of endocan, claudin-5 and cytokines in migraine. Eur Rev Med Pharmacol Sci. 2016;20(5):930-6.
4. Martami F, Jahromi SR, Togha M, Ghorbani Z, Seifishahpar M, Saidpour A. The serum level of inflammatory markers in chronic and episodic migraine: a case-control study. Neurological Sciences. 2018;39(10):1741-9.
5. MacGregor EA. Migraine. Ann Intern Med. 2017;166(7):Itc49-itc64.
6. Gryglas A, Smigiel R. Migraine and Stroke: What's the Link? What to Do? Curr Neurol Neurosci Rep. 2017;17(3):22.
7. Ramachandran R. Neurogenic inflammation and its role in migraine. Semin Immunopathol. 2018;40(3):301-14.
8. Celik A, Karayakali M, Altunkas F, Karaman K, Arisoy A, Ceyhan K, et al. Red cell distribution width is correlated with extensive coronary artery disease in patients with diabetes mellitus. Cardiovascular journal of Africa. 2017;28(5):319.
9. Khani M, Karimi Z. Prognosis of Chronic Myeloid Lymphoma with Red Cell Distribution Width. J Blood Res. 2018;1(1):5.
10. Öztürk ZA, Ünal A, Yiğiter R, Yesil Y, Kuyumcu ME, Neyal M, et al. Is increased red cell distribution width (RDW) indicating the inflammation in Alzheimer's disease (AD)? Archives of gerontology and geriatrics. 2013;56(1):50-4.
11. Zhang T, Li J, Lin Y, Yang H, Cao S. Association Between Red Blood Cell Distribution Width and All-cause Mortality in Chronic Kidney Disease Patients: A Systematic Review and Meta-analysis. Arch Med Res. 2017;48(4):378-85.
12. Peng YF, Cao WY, Zhang Q, Chen D, Zhang ZX. Assessment of the Relationship Between Red Cell Distribution Width and Multiple Sclerosis. Medicine (Baltimore). 2015;94(29):e1182.
13. Aktas G, Sit M, Dikbas O, Tekce BK, Savli H, Tekce H, et al. Could red cell distribution width be a marker in Hashimoto's thyroiditis? Exp Clin Endocrinol Diabetes.2014;122(10):572-4.
14. Goyal H, Lippi G, Altin Gjymishka BJ, Chhabra R, May E. Prognostic significance of red blood cell distribution width in gastrointestinal disorders. World journal of gastroenterology. 2017;23(27):4879.
15. Zhang Z, Chew GM, Shikuma CM, Gangcuangco LMA, Souza SA, Shiramizu B, et al. Red blood cell distribution width as an easily measurable bio-

marker of persistent inflammation and T cell dysregulation in antiretrovirally treated HIV-infected adults. HIV clinical trials. 2018;19(5):172-6.
16. Lippi G, Cervellin G, Mattiuzzi C. Migraine and erythrocyte biology: a review. International journal of laboratory hematology. 2014;36(6):591-7.
17. Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G. Red blood cell distribution width: A simple parameter with multiple clinical applications. Critical reviews in clinical laboratory sciences. 2015;52(2):86-105.
18. Pamuk GE, Top MŞ, Uyanık MŞ, Köker H, Akker M, Ak R, et al. Is iron-deficiency anemia associated with migraine? Is there a role for anxiety and depression? Wiener klinische Wochenschrift. 2016;128(8):576-80.
19. Albury CL, Stuart S, Haupt LM, Griffiths LR. Ion channelopathies and migraine pathogenesis. Mol Genet Genomics. 2017;292(4):729-39.
20. Palm-Meinders IH, Koppen H, Terwindt GM, Launer LJ, van Buchem MA, Ferrari MD, et al. Iron in deep brain nuclei in migraine? CAMERA follow-up MRI findings. Cephalalgia. 2017;37(8):795-800.
21. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33(9):629-808.
22. Houts CR, McGinley JS, Wirth RJ, Cady R, Lipton RB. Reliability and validity of the 6-item Headache Impact Test in chronic migraine from the PROMISE-2 study. Quality of Life Research. 2021;30(3):931-43.
23. Celikbilek A, Zararsiz G, Atalay T, Tanik N. Red cell distribution width in migraine. International journal of laboratory hematology. 2013;35(6):620-8.
24. Arregui A, Leon-Velarde F, Cabrera J, Paredes S, Vizcarra D, Umeres H. Migraine, polycythemia and chronic mountain sickness. Cephalalgia. 1994;14(5):339-41.
25. Hermans H, Post MC, Thijs V, Spaepen M, Budts WI. Increased prevalence of migraine in adult congenital heart disease. Heart. 2007;93(3):361-2.
26. Forcelini CM, Dantas DC, Luz C, Santin R, Stein AT, Barros HM, et al. Analysis of leukocytes in medication-overuse headache, chronic migraine, and episodic migraine. Headache: The Journal of Head and Face Pain. 2011;51(8):1228-38.
27. Stovner L, Hagen K, Waage A, Bjerve K. Hereditary haemochromatosis in two cousins with cluster headache. Cephalalgia. 2002;22(4):317-9.
28. Gaul C, Krummernerl P, Tamke B, Kornhuber M. Chronic daily headache in hereditary hemochromatosis treated by venesection. Headache: The Journal of Head and Face Pain. 2007;47(6):926-8.
29. Sevindik MS, Demirci S, Göksan B, Özge A, Savrun FK, Onur H, et al. Accompanying migrainous features in pediatric migraine patients with restless legs syndrome. Neurological Sciences. 2017;38(9):1677-81.
30. Eidlitz-Markus T, Zolden S, Haimi-Cohen Y, Zeharia A. Comparison of comorbidities of migraine and tension headache in a pediatric headache clinic. Cephalalgia. 2017;37(12):1135-44.
31. Calhoun AH, Gill N. Presenting a New, Non-Hormonally Mediated Cyclic Headache in Women: End-Menstrual Migraine. Headache: The Journal of Head and Face Pain. 2017;57(1):17-20.

Author Contribution: All the listed authors were substantially involved in the preparation of the manuscript. All authors have approved the final version of the manuscript.

Funding statement: No funding was available to this work.

Acknowledgements: None.