

Basophil and Eosinophil Counts May Give Clues in the Differential Diagnosis of Carotid Artery Disease and Vasculitis: A Comparative Study

Karotid Arter Hastalığı ve Vaskülitin Ayırıcı Tanısında Bazofil ve Eosinofil Sayıları İpuçları Verebilir: Karşılaştırmalı Bir Çalışma

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Keywords

Carotid artery disease, vasculitis, eosinophil, basophil

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Abstract

Objective: This study aimed to investigate if there is any difference in terms of leukocyte and platelet counts between vasculitis and cerebral thromboembolism.

Materials and Methods: In this cross-sectional study, the records of patients who underwent diagnostic cerebral angiography at Aydın Adnan Menderes University Hospital between January 2017 and December 2020 were recorded retrospectively. One hundred fifty-nine patients were included in this study. One hundred twenty-nine patients have the diagnosis carotid artery disease (CAD group) in varying degrees and 30 patients have the diagnosis of vasculitis (vasculitis group).

Results: Fifty-five (34.6%) patients were women and 104 (65.4%) were men. The median (1st quartile-3rd quartile) age was 67 (56-75). In the atherosclerosis group, 14.7% minimal occlusion (occlusion level: 20-49%), 15.5% moderate occlusion (occlusion level: 50-70%), 69.8% severe occlusion (occlusion level: 75-100%) were detected. The age is significantly higher in the CAD group than in the vasculitis group ($p<0.001$). Also, eosinophil ($p=0.028$) and basophil ($p<0.001$) levels were significantly higher, platelet level was significantly lower in the atherosclerosis group than in the vasculitis group. The comparison is done according to gender. There are significantly higher eosinophil ($p=0.007$) and basophil ($p=0.006$) levels in male patients with atherosclerosis than in male patients with vasculitis but not in females.

Conclusion: Compared with vasculitis cases, basophil and eosinophil levels were higher and platelet levels were lower in CAD cases. In cases with suspected CAD, higher eosinophil and basophil levels, and lower thrombocyte levels may be clues in terms of diagnosis and may guide clinicians in early diagnosis.

Öz

Amaç: Bu çalışmanın amacı, vaskülit ve serebral tromboemboli arasında lökosit ve trombosit sayıları açısından fark olup olmadığını araştırmaktır.

Gereç ve Yöntemler: Bu kesitsel çalışmada, Aydın Adnan Menderes Üniversitesi Hastanesi'nde Ocak 2017-Aralık 2020 tarihleri arasında tanısız serebral anjiyografi yapılan hastaların kayıtları geriye dönük olarak kaydedildi. Bu çalışmaya 159 hasta dahil edildi. Yüz yirmi dokuz hastaya değişen derecelerde karotis arter hastalığı (KAH grubu), 30 hastaya vaskülit (vaskülit grubu) tanısı konmuştur.

Bulgular: Hastaların 55'i (%34,6) kadın, 104'ü (%65,4) erkekti. Ateroskleroz grubunda, ortanca (1. çeyrek-3. çeyrek) yaş 67 (56-75) idi. %14,7 minimal oklüzyon

(tıkanma seviyesi: %20 ila %49), %15,5 orta oklüzyon (oklüzyon seviyesi: %50 ila %70) ve %69,8 ciddi oklüzyon (oklüzyon seviyesi: %75 ila %100) tespit edildi. KAH grubunda yaş vaskülit grubuna göre anlamlı olarak daha yüksektir ($p<0,001$). Ayrıca ateroskleroz grubunda vaskülit grubuna göre eozinofil ($p=0,028$) ve bazofil ($p<0,001$) düzeyleri anlamlı olarak yüksek, trombosit düzeyi anlamlı olarak düşüktü. Karşılaştırma cinsiyete göre yapıldı. Aterosklerozlu erkek hastalarda eozinofil ($p=0,007$) ve bazofil ($p=0,006$) seviyeleri vaskülitik erkeklere göre anlamlı olarak daha yüksekti, ancak kadınlarda yoktu.

Sonuç: Vaskülit olguları ile karşılaştırıldığında, KAH vakalarında bazofil ve eozinofil seviyeleri daha yüksek ve trombosit seviyeleri daha düşüktü. KAH şüphesi olan olgularda eozinofil ve bazofil düzeylerinin artması, trombosit düzeylerinin düşmesi tanı açısından ipucu olabilir ve klinisyene erken tanıda yol gösterici olabilir.

Introduction

Stroke is a neurological disorder and the second leading cause of death. It is caused by impaired perfusion due to blockage of blood vessels to the brain. The most common reason for stroke is atherosclerosis which is a disease of arteries and characterized by abnormal accumulation of lipids, inflammatory cells, matrix deposits. Inflammation plays an important role in the process of plaque rupture and the formation of thrombosis (1). Similar to atherosclerosis, vasculitis involving large vessels such as giant cell arteritis affect the vascular endothelium, causing vessel narrowing, occlusion, and various clinical findings related to these effects. In particular, ischemia as a result of these diseases may be life-threatening (2). On the other hand, the incidence of atherosclerosis increases with age (3).

Eosinophils and basophils are involved in the pathogenesis of vasculitis (4). Eosinophils are specialized inflammatory cells that routinely measured as part of the complete blood cell count. Brain infarcts due to thromboembolism are said to be associated with the toxicity of eosinophils (5). Eosinophils promote atherosclerosis involving von Willebrand factor (VWF) exposure on endothelial cells and increased atherogenic platelet adhesion to the vessel wall. Once arterial thrombosis is triggered, eosinophils are rapidly recruited to the lesion site in an integrin-dependent manner and intensively interact with platelets resulting in propagation and stabilization of developing thrombi (6). Basophils are a small fraction of leukocytes and secrete heparin and histamine. There is a significant relationship between the low basophil count as well as the basophilic percent in the blood picture with common thrombotic problems namely the deep vein thrombosis (7). However, Nemec et al. (8) found an increase in basophil count with a higher dose of anticoagulant compared to low dose anticoagulant in dogs but this finding didn't reach significance.

In various studies, the use of imaging methods for the differential diagnosis of atherosclerosis and vasculitis has been examined, and it has been emphasized that these two diseases can be differentiated with various imaging methods (9). To the best of our knowledge, there is no study examining various biomarkers and presenting evidence-based results on this subject. The aim of this study was to investigate if there is any difference in terms of leukocyte and platelet counts between vasculitis and cerebral thromboembolism.

Materials and Methods

In this cross-sectional study, the records of patients who underwent diagnostic cerebral angiography at Aydın Adnan Menderes University Hospital between January 2017 and December 2020 were recorded retrospectively. Ethical approval of the study was obtained from the Aydın Adnan Menderes University Ethics Committee (protocol no: 2021/101, date: 10.06.2021).

Study Group

All cases meeting the inclusion criteria were included in the study by examining the cerebral angiographies performed on the relevant dates.

Inclusion criteria:

- Over the age of 18,
- Those with carotid artery disease (CAD) that is diagnosed as narrowing or near complete or complete blockage of vessels due to plaques during digital subtraction angiography.
- Patients with small-medium sized vasculitis of central nervous system which is demonstrated by the presence of vessel stenoses or aneurysms during digital subtraction angiography.

Exclusion criteria:

- Cases that did not meet the inclusion criteria,
- Presence of active infection, chronic inflammatory disease, severe allergy

Finally, 159 patients were included in this study. One hundred twenty-nine patients have the diagnosis CAD in varying degrees and 30 patients have the diagnosis of vasculitis.

Variables

In our study, the following parameters were examined

- Sociodemographic characteristics (gender, age),
- The result of angiography (vascular occlusion degree),
- Blood sample results (the count of leukocyte, neutrophil, lymphocyte, monocyte, eosinophil, basophil, platelet),
- Monocyte/lymphocyte ratio,
- Platelet/lymphocyte ratio,
- Neutrophil/lymphocyte ratio.

Procedure of the Study

The blood samples of cases who applied to our clinic and underwent cerebral angiography were retrospectively screened.

Statistical Analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). For the normality check, the Shapiro-Wilk test was used. Data are given as (interquartile range; IQR) for continuous variables according to the

normality of distribution and frequency (percentage) for categorical variables. Non-normally distributed variables were analyzed with the Mann-Whitney U test. Categorical variables were evaluated using the chi-square tests. Two-tailed p-values of less than 0.05 were considered statistically significant.

Results

Fifty five (34.6%) patients were women and 104 (65.4%) were men. The median (IQR) age was 67 (56-75). In the atherosclerosis group, 14.7% minimal occlusion (occlusion level: 20% to 49%), 15.5% moderate occlusion (occlusion level: 50% to 70%), 69.8% severe occlusion (occlusion level: 75% to 100%) were detected. The age is significantly higher in the CAD group than in the vasculitis group ($p < 0.001$). Also, eosinophil ($p = 0.028$) and basophil ($p < 0.001$) levels were significantly higher, platelet level was significantly lower in the atherosclerosis group than the vasculitis group. The comparison is done according to gender. There are significantly higher eosinophil ($p = 0.007$) and basophil ($p = 0.006$) levels in male patients with atherosclerosis than male patients with vasculitis but not in females (Table 1).

Table 1. Summary of patients' characteristics with regard to groups

	Carotid artery disease (n=129)	Vasculitis (n=30)	p-value
Gender			
Male	87 (67.4%)	17 (56.7%)	0.264
Female	42 (32.6%)	13 (43.63%)	-
Age (year)	68.5 (62-76)	45.5 (38-53)	<0.001
Vascular occlusion (%)	85 (65-95)	0 (0-0)	-
Leukocyte (x10 ³ /mL)	8.75 (7.33-10.23)	8.60 (7.50-11.26)	0.528
Neutrophil (x10 ³ /mL)	5.44 (4.47-7.29)	5.57 (4.46-8.26)	0.644
Lymphocyte (x10 ³ /mL)	2.06 (1.54-2.61)	1.99 (1.44-2.86)	0.681
Monocyte (x10 ³ /mL)	0.57 (0.44-0.72)	0.48 (0.41-0.63)	0.108
Eosinophil (x10 ³ /mL)	0.14 (0.09-0.24)	0.10 (0.04-0.20)	0.028
Basophil (x10 ³ /mL)	0.03 (0.02-0.05)	0.02 (0.02-0.03)	<0.001
Platelet (x10 ³ /mL)	243 (194-290)	269.5 (247-310)	0.012
Monocyte/lymphocyte	0.26 (0.18-0.39)	0.24 (0.19-0.27)	0.202
Platelet/lymphocyte	121.68 (88.45-167.14)	132.06 (105.44-184.06)	0.509
Neutrophil/lymphocyte	2.92 (1.96-4.22)	3.04 (2.00-3.8)	0.925
Data are given as median (1 st quartile-3 rd quartile) for continuous variables and as frequency (percentage) for categorical variables			

Discussion

Atherosclerosis and vasculitis, which are diseases with inflammation in large and small vessels, may present with clinically similar symptoms. In this study, in which the clinical features of cases diagnosed with vasculitis and different degrees of CAD were compared, basophil and eosinophil cells levels were significantly higher and platelet levels were significantly lower in CAD cases when compared with vasculitis cases.

For years, eosinophils have been known as cells involved in parasitic infection and allergy. However, today it is emphasized that eosinophils have an important role in immunoregulation. Eosinophils continue to be examined for their specific roles in various studies (10,11). In this study, we determined that CAD cases had significantly higher eosinophil levels when compared to vasculitis cases. There are similar results on this subject in the literature. Madjid et al. (12) suggested that the development of cardiovascular events originating from atherosclerosis in the future can be predicted by the level of eosinophil. Tanaka et al. (13) reported a relationship between the level of eosinophils and the severity of coronary heart disease and vascular stenosis. Similarly, different studies have shown a correlation between eosinophil level and the risk of atherosclerotic disease (14,15). The reason for this relationship has not been fully revealed in the studies. In a study examining the reasons for the association of eosinophil level with atherosclerotic events and the development of thrombosis, Marx et al. (6) showed that an increase in eosinophil level increases the exposure of VWF and platelet adhesion in the endothelium. As a result of their studies, the authors underlined that eosinophil is a promising parameter in terms of atherosclerotic events and thrombosis risk. On the other hand, an increase in eosinophil level was also shown in vasculitis cases (7). There has been no previous study comparing eosinophil values between vasculitis and CAD cases. Therefore, the difference between the groups detected in our study could not be compared with the results of other studies.

Basophils, like eosinophils, are another type of leukocyte that has an important role in the immune system. Various studies have investigated the relationship between basophil level and atherosclerotic diseases and vasculitis. Pizzolo et

al. (16) emphasized that basophil level is associated with factor II plasma coagulant activity in coronary artery disease and is important in the development of thrombosis. The relationship between atherosclerosis in the coronary artery and basophil level has also been shown in different studies (17). It has been suggested that basophils may play a role in the increase of extracellular DNA traps, polyphosphate, and platelet-activating factors, which can trigger coagulation and thrombosis. Studies focus on the fact that basophil can be effective in increasing thrombosis and coagulation through these pathways (18,19). Although there are studies on the role of basophil in the pathogenesis of vasculitis, this conclusion could not be reached clearly (20). In our study, basophil level was found to be higher in CAD cases when compared with vasculitis cases. In previous studies, basophil levels were not compared between vasculitis and atherosclerotic diseases. Therefore, we believe that the results of our study are valuable.

In the case of vascular damage, steps that result in platelet adhesion, activation, and aggregation are triggered. When the atherosclerotic vessel is mechanically damaged or the plaque ruptures, the blood encounters thrombogenic substances, and platelets are involved in this pathophysiological process (21). After vascular damage, platelets migrate to the area of endothelial damage and form a hemostatic plaque. The next process depends on the ability of the platelets to bind to the subendothelial matrix, and the rapid shape and biochemical changes of the platelets. Available data on the role of platelets in the development of human atherosclerosis indicate that platelet activation is increased in coronary artery disease, transplant vasculopathy, and CAD (22). It has been reported that platelet activation is associated with increased wall thickness in the carotid artery. In addition, some platelet-derived chemokines and growth factors have been found in atherosclerotic plaques. Antiplatelet drugs are thought to be ineffective in preventing the progression of atherosclerosis (22). It has been shown that the platelet level is significantly reduced in ischemic conditions (23). In addition, it has been emphasized that there may be a relationship between the prognosis of ischemic diseases and the platelet level (24). On the other hand, the relationship between vasculitis and platelet level was also investigated, and

it was found that platelet level may increase in active vasculitis involving small vessels (25). Based on the studies on vasculitis and atherosclerosis (although the platelet level was not compared between vasculitis and CAD cases in previous studies), we can say that we found lower platelet levels in vasculitis cases and higher in CAD cases in accordance with the literature.

This study has many limitations. The single-center nature of the study limits its generalizability. The retrospective collection of data limited the inclusion of additional variables in the study. Many parameters that may affect the presence of atherosclerosis, the presence of vasculitis and routine blood values (including basophils and eosinophils) are not examined. The effects of these parameters at different levels led us to misinterpret our results. Asymptomatic or undiagnosed atherosclerosis or vasculitis in the different vessels of the subjects are not evaluated. Pathologies found in different vessels may have an effect on the results. Additional diseases and drugs used are not recorded. Furthermore, healthy controls were not involved in this study. These situations may led us to interpret the results more negatively or positively. The vasculitis subtype was not recorded and subtype-specific analyzes are not performed. Eosinophil and basophil levels may differ in different vasculitis subtypes. Since the older results of the cases are not evaluated in our study, a cause-and-effect interpretation can not be made. The differences mentioned may occurred before or after the diseases.

Conclusion

Compared with vasculitis cases, basophil and eosinophil levels were higher and platelet levels were lower in CAD cases. In cases with suspected CAD, increased eosinophil and basophil levels, and decreased thrombocyte levels may be clues in terms of diagnosis and may guide clinicians in early diagnosis. In this way, clinicians can reduce the mortality and morbidity rates associated with this life-threatening disease by applying the necessary treatment in the earlier period. By examining more cases and more parameters in future studies, the role of basophil and eosinophil levels in the pathogenesis of CAD can be revealed in detail.

Ethics

Ethics Committee Approval: The present cohort study was designed as a survey and was approved

by the Clinical Research Ethics Committee of Aydın Adnan Menderes University (protocol no: 2021/101, date: 10.06.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

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References

1. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. *Circ Res* 2014; 114: 1852-66.
2. Jennette JC. Overview of the 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. *Clin Exp Nephrol* 2013; 17: 603-6.
3. Head T, Daunert S, Goldschmidt-Clermont PJ. The Aging Risk and Atherosclerosis: A Fresh Look at Arterial Homeostasis. *Front Genet* 2017; 8: 216.
4. Moyer CF, Jerome WG, Taylor R, Tulli H, Reinisch CL. Autoimmune vasculitis in MRL/Mp-lpr/lpr mice: orthochromatic basophils participate in the development of delayed-type hypersensitivity angiitis. *Autoimmunity* 1992; 12: 159-65.
5. Sarazin M, Caumes E, Cohen A, Amarenco P. Multiple microembolic borderzone brain infarctions and endomyocardial fibrosis in idiopathic hypereosinophilic syndrome and in *Schistosoma mansoni* infestation. *J Neurol Neurosurg Psychiatry* 2004; 75: 305-7.
6. Marx C, Novotny J, Salbeck D, Zellner KR, Nicolai L, Pekayvaz K, et al. Eosinophil-platelet interactions promote atherosclerosis and stabilize thrombosis with eosinophil extracellular traps. *Blood* 2019; 134: 1859-72.
7. Naser HA. Basophil count as predictor to the deep vein thrombosis and the thrombo-embolization. *Muthanna Medical Journal* 2018; 5: 95-106.
8. Nemeč A, Drobnič-Košorok M, Butinar J. The effect of high anticoagulant k3-edta concentration on complete blood count and white blood cell differential counts in healthy beagle dogs. *Slov Vet Res* 2005; 42: 65-70.
9. Nienhuis PH, van Praagh GD, Glaudemans AWJM, Brouwer E, Slart RHJA. A Review on the Value of Imaging in Differentiating between Large Vessel Vasculitis and Atherosclerosis. *J Pers Med* 2021; 11: 236.
10. Liao W, Long H, Chang CC, Lu Q. The Eosinophil in Health and Disease: from Bench to Bedside and Back. *Clin Rev Allergy Immunol* 2016; 50: 125-39.
11. Hellmark T, Ohlsson S, Pettersson Å, Hansson M, Johansson ACM. Eosinophils in anti-neutrophil cytoplasmic antibody associated vasculitis. *BMC Rheumatology* 2019; 3: 1-12.
12. Madjid M, Awan I, Willerson JT, Casscells SW. Leukocyte count and coronary heart disease: implications for risk assessment. *J Am Coll Cardiol* 2004; 44: 1945-56.
13. Tanaka M, Fukui M, Tomiyasu K, Akabame S, Nakano K, Yamasaki M, et al. Eosinophil count is positively correlated with coronary artery calcification. *Hypertens Res* 2012; 35: 325-8.

14. Niccoli G, Ferrante G, Cosentino N, Conte M, Belloni F, Marino M, et al. Eosinophil cationic protein: A new biomarker of coronary atherosclerosis. *Atherosclerosis* 2010; 211: 606-11.
15. Niccoli G, Cosentino N. Eosinophils: a new player in coronary atherosclerotic disease. *Hypertens Res* 2012; 35: 269-71.
16. Pizzolo F, Castagna A, Olivieri O, Girelli D, Friso S, Stefanoni F, et al. Basophil Blood Cell Count Is Associated With Enhanced Factor II Plasma Coagulant Activity and Increased Risk of Mortality in Patients With Stable Coronary Artery Disease: Not Only Neutrophils as Prognostic Marker in Ischemic Heart Disease. *J Am Heart Assoc* 2021; 10: e018243.
17. Morshed M, Hlushchuk R, Simon D, Walls AF, Obata-Ninomiya K, Karasuyama H, et al. NADPH oxidase-independent formation of extracellular DNA traps by basophils. *J Immunol* 2014; 192: 5314-23.
18. Yousefi S, Morshed M, Amini P, Stojkov D, Simon D, von Gunten S, et al. Basophils exhibit antibacterial activity through extracellular trap formation. *Allergy* 2015; 70: 1184-8.
19. Cromheecke JL, Nguyen KT, Huston DP. Emerging role of human basophil biology in health and disease. *Curr Allergy Asthma Rep* 2014; 14: 408.
20. Badimon L, Padró T, Vilahur G. Atherosclerosis, platelets and thrombosis in acute ischaemic heart disease. *Eur Heart J Acute Cardiovasc Care* 2012; 1: 60-74.
21. Kaplan ZS, Jackson SP. The role of platelets in atherothrombosis. *Hematology Am Soc Hematol Educ Program* 2011; 2011: 51-61.
22. Gawaz M, Langer H, May AE. Platelets in inflammation and atherogenesis. *J Clin Invest* 2005; 115: 3378-84.
23. Ranjith MP, Divya R, Mehta VK, Krishnan MG, KamalRaj R, Kavishwar A. Significance of platelet volume indices and platelet count in ischaemic heart disease. *J Clin Pathol* 2009; 62: 830-3.
24. Zheng X, Guo D, Peng H, Zhong C, Bu X, Xu T, et al. Platelet counts affect the prognostic value of homocysteine in acute ischemic stroke patients. *Atherosclerosis* 2019; 285: 163-9.
25. Willeke P, Kümpers P, Schlüter B, Limani A, Becker H, Schotte H. Platelet counts as a biomarker in ANCA-associated vasculitis. *Scand J Rheumatol* 2015; 44: 302-8.