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Complete Blood Count in Multiple Sclerosis

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Review

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ABSTRACT

Multiple sclerosis (MS) is a chronic disease that affects the central nervous system in primarily young adults. Although the exact etiology of MS is unknown, autoimmune mechanisms are thought to play a crucial role, especially with CD4+ T cells involved in the immune response. Inflammatory reactions involving T cells and macrophages are commonly observed in MS lesions. B lymphocytes, plasma cells, and antibodies also contribute to MS pathogenesis. Neutrophils, lymphocytes, monocytes, and platelets, key immune system components, play roles in inflammatory processes, but their association with MS prognosis remains inconclusive. Due to its heterogeneous nature, clinical manifestations of MS vary depending on the location of the affected central nervous system. While several potential biomarkers have been identified for MS diagnosis and monitoring, none have been universally accepted. Studies have examined complete blood count parameters in MS patients, including erythrocyte, platelet, and leukocyte populations. Changes in these parameters have been observed in MS patients compared to healthy controls and may be related to disease prognosis. For example, increased erythrocyte fragility and altered hemoglobin levels have been reported in MS patients. Leukocyte counts and ratios, such as the neutrophil/lymphocyte ratio, have shown associations with disease severity. Platelet activation and interaction with immune cells have also been implicated in MS pathophysiology. Nevertheless, further research is needed to fully understand the role of complete blood count parameters in MS. Identifying reliable biomarkers for early diagnosis and prognosis prediction would greatly enhance MS management. Moreover, these benefits could lead to substantial improvements in achieving complete recovery of patients, surpassing the focus on current symptomatic treatments.

Keywords: Complete Blood Count, Multiple Sclerosis, Immune System

Multipl Sklerozda Tam Kan Sayımı

Derleme

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ÖZET

Multipl skleroz (MS), öncelikle genç yetişkinlerde görülen ve merkezi sinir sistemini etkileyen kronik bir hastalıktır. MS'nin etiyolojisi tam olarak bilinmemekle birlikte, immün yanıtta önemli görevleri olan CD4+ T hücrelerini içeren otoimmün mekanizmaların rol oynadığı düşünülmektedir. T hücreleri ve makrofajların dahil olduğu inflamatuar reaksiyonlar, MS lezyonlarında yaygın olarak görülür. B lenfositleri, plazma hücreleri ve antikorlar da MS patogenezine katkıda bulunur. Temel bağışıklık sistemi bileşenleri olan nötrofiller, lenfositler ve monositlere ek olarak trombositler de inflamatuar süreçlerde rol oynar, ancak bu hücrelerin MS prognozu ile ilişkileri kesin değildir. Heterojen doğası nedeniyle, MS'nin klinik belirtileri etkilenen merkezi sinir sisteminin konumuna bağlı olarak değişir. MS tanı ve takibi için birkaç potansiyel biyobelirteç tanımlanmış olsa da bunların hiçbiri evrensel olarak kabul edilmemiştir. Çalışmalar, MS hastalarında eritrosit, trombosit ve lökosit popülasyonları dahil olmak üzere tam kan sayımı parametrelerini incelemiştir. MS hastalarında sağlıklı kontrollere kıyasla kan sayımı testlerinde gözlenen değişiklikler, hastalık prognozu ile ilişkili olabilir. Örneğin, MS hastalarında eritrosit frajilitesinde artış ve hemoglobin seviyelerinde değişiklikler bildirilmiştir. Lökosit sayıları ve nötrofil/lenfosit oranının hastalık şiddeti ile ilişkili olduğu gösterilmiştir. Trombosit aktivasyonu ve immün hücrelerle etkileşim de MS patofizyolojisine katkıda bulunmaktadır. Bununla birlikte, MS'de tam kan sayımı parametrelerinin rolü üzerine kesin bilgiler sağlamak için bu alandaki çalışmaların genişletilmesine ihtiyaç vardır. Erken tanı ve prognoz tahmini için güvenilir biyobelirteçlerin tanımlanması, MS hastalarını yönetimini büyük ölçüde geliştirecektir. Dahası, bu faydalar, mevcut semptomatik tedavilere odaklanmanın ötesine geçerek hastaların iyileşmesini sağlamada önemli gelişmelere yol açabilir.

Anahtar Kelimeler: Tam Kan Sayımı, Multipl Skleroz, Bağışıklık Sistemi

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Introduction

Multiple sclerosis (MS) is a chronic disease characterized by diffuse demyelinating lesions in the central nervous system (CNS), often affecting young adults. Although the underlying exact mechanisms is unknown, autoimmunity are thought to play a role in its etiopathogenesis.[1] MS is a highly heterogeneous disease and patients may present with various clinical manifestations including motor and sensory loss and autonomic disorders depending on the area of the central nervous system affected.[2] Clinical findings vary according to the localization and extent of demyelinating lesions.[3] In general, there are three types of MS: Relapsing-remitting multiple sclerosis (RRMS), Primary Progressive Multiple Sclerosis (PPMS) and Secondary Progressive Multiple Sclerosis (SPMS).[3,4] There is no proven curative treatment for MS yet, so current treatments are of a temporary nature, such as reducing the frequency of attacks and alleviating symptoms.[5] Although many biomarkers that are thought to be used in diagnosis and follow-up have been defined, a reliable and generally accepted marker has not yet been identified in the studies conducted to date.[6,7]

Immune system is classified as the innate and acquired immune system. The components of the innate immunity respond very quickly to changes in homeostasis, whereas the acquired immune response takes time and is much more specific.[8] The cellular components of innate immunity are natural killer (NK) cells, macrophages, monocytes, and neutrophils. T and B lymphocytes, which are the main cellular components of acquired immunity, specifically recognize, proliferate and activate against a pathogen.[9] The importance of the innate and acquired immune system in the MS pathogenesis is indisputable. $CD4^+$ T cells take the first place in the immune response in MS.[10] T lymphocytes produce immune activation against other myelin antigens, especially myelin basic protein (MBP).

Although pathological examination of MS lesions has revealed different mechanisms in the development of demyelination, inflammatory reactions caused by T lymphocytes and macrophages have been found in the majority of lesions.[11] In addition, B lymphocytes, plasma cells, and antibodies are also thought to play a role in the pathogenesis of MS. It is also well known that neutrophils, lymphocytes, monocytes, and platelets, which are important elements of the immune system, are effective in the control of systemic inflammation and undergo changes in inflammation processes. Although studies conducted with MS patients, have suggested that neutrophil, lymphocyte, platelet, and monocyte counts may be associated with prognosis, no definitive conclusion has been reached.[6,7]

In this review, we evaluated the findings of some studies in which complete blood count parameters (neutrophil, lymphocyte, erythrocyte, platelet, and monocyte populations) were examined in MS patients.

Complete Blood Count

The complete blood count (CBC) or hemogram, is a test that allows us to obtain information about the number of cells in the blood, their percentages, and some characteristics of these cells. The comparison of measurement methods used by different analyzers is given in Table 1.

In a complete blood count, erythrocyte, platelet, and leukocyte counts and indices are determined by direct measurement or calculation. One of the measurement methods is flow cytometry. It is a technology used to measure multiple properties of a single cell (or bacteria etc.) simultaneously at high speed. Flow cytometry consists of three systems: a channel system, an optical system, and an electrical system, which detects light and fluorescence scattered from cells. This provides information about the size, cell membrane, cytoplasm, and nucleus of leukocytes and subgroups.[12] These data help us to learn about many inflammatory and non-inflammatory changes. While optical methods are used for leukocyte counts, erythrocytes and platelets are counted by impedance method.

Erythrocytes count, mean corpuscular volume (MCV), hematocrit (HCT), hemoglobin (HB), mean hemoglobin concentration (MCH), red blood cell distribution (RDW), and nucleated red blood cells (NRBC) data provide information about erythropoiesis function. Platelet (PLT), mean platelet volumes (MPV), platelet width (PDW), and plateletcrit (PCT) values give us information about primary hemostasis. Reticulocyte count (RET) is a very valuable parameter in the evaluation of bone marrow response, especially for the differential diagnosis of anemia when MCV is normal. Neutrophils, eosinophils, basophils, monocytes, and lymphocytes play an important role in the diagnosis and follow-up of various inflammatory diseases.[13,14] Today's advanced devices can also count erythroblasts and immature granulocytes (IG). IG increases in sepsis and bacterial infections.[15]

Red Blood Cell (RBC)

Erythrocytes (or red blood cells) are disk-shaped, non-nucleated cells measured in the complete blood count. Their most important function is to transport oxygen and carbon dioxide between the tissues and the lungs. Hemoglobin is a tetrameric protein that contains two different globulin chains and fills almost the entire cell content. Through hemoglobin, erythrocytes bind oxygen in the lungs and deliver to the tissues, take carbon dioxide from the tissues and bring it back to the lungs. Reticulocytes are the nucleated intermediate cells observed during the maturation of erythrocytes.[16,17]

Recent studies and clinical observations show that hemoglobin and RBCs may play an important role in the pathogenesis of MS. It is stated that MS patients have higher erythrocyte fragility which leads to increased free Hb and damages the blood-brain barrier and myelin basic protein. It is also thought that increased iron levels will trigger inflammatory events.[18] In a study of 73 MS patients and 38 healthy controls, RBC osmotic fragility was reported to be

Table 1. Blood count parameters measurement methods of different devices.[12]

Parameter	Beckman Coulter UniCel DxH 800	Sysmex XN Series	Abbott CELL-DYN Sapphire	ADVIA 2120i	Mindray BC Series
WBC	Impedance	Fluorescent dye light scatter	Light scatter	Light scatter	Fluorescent dye light scatter
RBC	Impedance	Impedance	Impedance	Laser light scatter	Impedance
HGB	Cyanhemoglobin 525 nm	Sodium lauryl sulfate 555 nm	Cyanhemoglobin 540 nm	Cyanhemoglobin 546 nm	Cyanide-free photometric measurement
HCT	(RBC x MCV)/10	Total RBC pulse height	(RBC x MCV)/10	(RBC x MCV)/10	(RBC x MCV)/10
MCV	Derived from RBC Histogram	(Hct/RBC) x 10	Derived from RBC Histogram	(Hct/RBC) x 10	(Hct/RBC) x 10
MCHC	(HGB/HCT) x 100	(HGB/HCT) x 100	(HGB/HCT) x 100	(HGB/HCT) x 100	(HGB/HCT) x 100
RET	Supravital staining light scatter	Fluorescent dye light scatter	Supravital staining light scatter	Fluorescent dye light scatter	Fluorescent dye light scatter
PLT	Light scatter and impedance	Light scatter and impedance	Light scatter and impedance	Light scatter	Impedance

WBC: white blood cell, RBC: red blood cell. HGB: hemoglobin, Hct: hematocrit, MCV: mean corpuscular volume, MCHC: mean corpuscular hemoglobin concentration, RET: Reticulocyte, PLT: platelet.

significantly higher in patients than in controls.[19] Hon et al. reported that erythrocyte membrane fluidity was impaired in MS.[20] In another study, they reported an inverse correlation between RBC count and disease duration or disability status scale in MS patients. They also found that MS patients had significantly lower hemoglobin concentrations compared to healthy people.[21]

A study of 187 MS patients and 200 controls revealed significant differences in the prevalence of anemia between patients and controls. Furthermore, MS risk was seven times higher in anemic men and two times higher in anemic women.[22] Fingolimod is a highly effective immunomodulatory drug and the first oral treatment for relapsing-remitting MS. Among other mechanisms, it shows diverse therapeutic effects on cell survival, from inducing apoptosis to protecting against cell death. The use of fingolimod in MS patients has been demonstrated to reduce Hct, Hb, and RBC levels as well as lymphocytes and platelets.[23,24]

White Blood Cell

With the development of flow cytometer and radio waves method in complete blood count devices, the "5-part leukocyte differential" (neutrophils, eosinophils, basophils, monocytes and lymphocytes) could be determined. Neutrophils, one of the leukocyte groups, form the body's first line of defense against bacterial and viral infections and phagocytize microorganisms, dead tissues and debris. A decrease in neutrophils number, which constitute the majority of leukocytes, increases the risk of infection.[25] Eosinophils are especially involved in defense against parasitic infections and their numbers increase in allergic conditions together with basophils.[16] Monocytes are the circulating precursors of macrophages in tissues and the first cell to come into contact with the pathogen.[26] Lymphocytes are produced in the bone marrow like neutrophils and can fulfill their functions after the maturation process. B lymphocytes complete the maturation process in the lymphoid tissue associated with the digestive system and T lymphocytes in the thymus. They then pass into the bloodstream and some of them function in secondary lymphoid organs such as lymph nodes and spleen.[27,28]

Various studies have been conducted on the role of leukocytes and their subgroups in MS pathogenesis and their use as biomarkers. In a study of 127 MS patients divided into two groups (Expanded disability status scale, EDSS <5 (n=90) and EDSS ≥5 (n=37)) and a significant increase in neutrophil/lymphocyte (NLR) ratio was found in patients with EDSS ≥5. A high NLR ratio in MS was thought to increase inflammation and cause an elevated EDSS score.[29] Increased neutrophil activation is thought to be a result of the chronic inflammatory environment, according to Naegele et al.[30,31] Pierson et al. showed that neutrophils play a role in MS pathogenesis and that neutrophils number and activity are increased in Relapsing-Remitting MS patients in contrast to healthy controls. It is claimed that neutrophils contribute to MS pathogenesis by increasing cytokine production and causing damage to the blood-brain barrier.[32,33]

Akaishi et al. reported that leukocyte, monocyte, basophil, and neutrophil counts were higher in MS patients compared to healthy controls before treatment and during attacks. However, no difference was found in terms of lymphocyte levels. These results suggested that the immune system may be systemically altered from the early stages of MS and that innate immunity may play a role in some steps of disease development and progression.[34]

In another study on neutrophils and monocytes, which represent the first line of the innate immune system, leukocytes were phenotyped by flow cytometry, and it was found that granulocytes, $CD15^+$ neutrophils, and monocytes were enlarged while lymphocytes were decreased in relapsing-remitting MS patients. It was thought that the phenotype differences might help earlier diagnosis of these patient.[35]

Platelets

Platelets are one of the parameters investigated for MS and play a primary role in the pathophysiology of central nervous system diseases. Platelets, evaluated in hemogram tests, can activate leukocytes indirectly through biologically active compounds secreted from their granules or directly by binding to the receptor. They are the most numerous cells in the circulatory system after erythrocytes. It is thought that many cytokines and chemokines in their structure play an important role in hemostasis, inflammation, and leukocyte activation.[36] Recent studies have revealed that platelets contribute to the immune system and interact with other immune cells (neutrophils, macrophages, etc.). Since platelets in inflamed neural tissues can adhere to these immune cells, they may cause increased inflammation by recruiting leukocytes.[37-39] Starossom et al. suggested that platelets promote neuro-inflammation and contact with immune cells in MS.[40]

Platelets are the main effector cells in hemostasis, coagulation, and pathological thrombosis. As a result, their role in coagulation and inflammation may be associated with increased vascular risks in MS patients.[41] Additionally, changes in platelet RNA expression profiles were also detected in MS patients.[42] MS is a disease that affects only humans. However, researchers have identified several animal models that can cause MS. The most commonly used models are encephalomyelitis and the cuprizone model.[41] Langer et al. induced chronically activated demyelinating lesions in experimental encephalomyelitis animal models. Histological examinations of the brain and spinal cord showed that platelets accumulated in these lesions and platelet counts increased in the blood.[43]

In a different study involving 253 individuals (126 MS and 127 controls), leukocyte, lymphocyte, and neutrophil values were significantly lower in the MS group. In contrast, platelet volume (MPV), platelet distribution width (PDW), and platelets (PLT) were significantly higher.[44]

Conclusion

Early diagnosis and prediction of prognosis are vital for multiple sclerosis patients. Although studies have identified many biomarkers that could be used for these purposes, none have yet entered routine use. In this review, we examined some studies evaluating the relationship between complete blood count and MS. Accordingly, we found that some hematologic parameters showed variability in patients compared to healthy controls and may be associated with prognosis. However, despite all these studies, we believe that additional studies are needed on the changes in complete blood count parameters in MS. These factors will be more helpful in identifying and treating the condition in future studies.

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