Is Elevated Neutrophil-to-Lymphocyte Ratio a Predictor of Stroke in Patients with Intermediate Carotid Artery Stenosis?

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Objective: An increased neutrophil-to-lymphocyte ratio (NLR) is associated with poor clinical prognosis in patients with cardiovascular disease. In this study, we aimed to investigate if there was a correlation between NLR and the risk of stroke in patients with intermediate carotid artery stenosis. *Methods:* A total of 254 patients with a 50%-70% stenosis in the carotid artery, 115 of whom were symptomatic and 139 of whom were asymptomatic, were included in the study. Patients with a history of ischemic cerebrovascular event with or without sequelae, transient ischemic attack, and amaurosis fugax in the last 1-6 months were included in the symptomatic group of the study. The symptomatic and asymptomatic groups were compared in terms of total neutrophil count, lymphocyte count, and NLR. *Results:* The total white blood cell count (WBC), neutrophil count, and NLR were found to be higher and the lymphocyte count was found to be lower in the symptomatic patients than those in the asymptomatic patients (symptomatic/asymptomatic, respectively, WBC [10^3/mm^3]: 9.0/8.2, neutrophil count [10^3/mm^3]: 6.1/5.0, NLR: 3.08/2.2, lymphocyte count [10^3/mm^3]: 1.9/2.2) ($P < .001$). The cutoff value for NLR was found to be 2.6 or higher. In the multivariate regression analysis, an NLR value of 2.6 or higher was shown to be an independent variable for carotid artery stenosis to become symptomatic. *Conclusions:* NLR is increased in symptomatic intermediate carotid artery stenosis. An increased NLR value is an independent variable for carotid artery plaques to become symptomatic. **Key Words:** Atherosclerosis—carotid artery stenosis—inflammation—neutrophil-to-lymphocyte ratio—stroke.

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Introduction

Atherosclerotic lesions are an important cause of ischemic stroke worldwide,[1] accounting for approximately 10% of ischemic stroke cases in the United States and as much as 30%-40% of all incidents of ischemic stroke in Asia. Inflammation plays a role in all stages, from the onset of atherosclerosis to progression and subsequent rupture of the atherosclerotic plaque.[2,3] The main events in the physiopathology of atherogenesis are smooth muscle cell proliferation and lipid deposition in response to endothelial damage.[4] Until recently, T lymphocytes and monocytes were considered to play prominent roles in atherogenesis as inflammatory cells. The significance of neutrophils was later demonstrated through observation of neutrophils in the atherosclerotic plaques of carotid arteries.[5] Detection of early neutrophil infiltration in the atherosclerotic plaques allows prediction of the risk of plaque rupture.[6,7] Neutrophil predominance was demonstrated in rupture-prone lesions (larger lipid core, heavy macrophage influx, minor collagen, and smooth muscle cells) and neutrophils were shown to play a significant role in

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plaque destabilization.[8,9] A high rate of neutrophil elastase activity was also reported in histological investigations of the late-stage plaques formed in cerebral arteries.[10]

Neutrophils also affect platelets and increase aggregation.[11] Activated neutrophils lead to plaque rupture through the effects of various proteolytic enzymes and myeloperoxidase-like oxidants.[12,13] In addition, neutrophils stimulate thrombogenesis by releasing tissue factors or inducing other cells to release tissue factors.[14,15] Currently, neutrophil-to-lymphocyte ratio (NLR) is considered to be a good marker that simultaneously shows the negative effects of neutrophil elevation as an indicator of acute inflammation and lymphocyte depletion as an indicator of physiological stress, as well as aids in the prediction of mortality and prognosis in stroke patients.[16,17]

Severity of a carotid artery lesion is an important parameter that affects the risk of stroke. The risk of stroke increases with the severity of carotid artery lesion.[18] To perform carotid artery intervention, the level of stenosis should angiographically be at least 50% in symptomatic patients and at least 70% in asymptomatic patients.[19] In symptomatic patients, plaques that cause up to 50% stenosis in the carotid artery may pose a risk of recurrent stroke and requires surgical intervention or placement of a stent. We believe that a part of the plaques that cause asymptomatic intermediate carotid artery stenosis (50%-70%) may be associated with a higher risk of stroke. In this study, symptomatic and asymptomatic patients with intermediate carotid artery stenosis were compared in terms of total neutrophil count, lymphocyte count, and NLR.

Materials and Methods

Study Population

A total number of 312 patients were evaluated between December 2010 and January 2015 for enrollment in this prospective study. Fifty-eight patients were excluded from the study due to different causes and analyses were performed on the data obtained from 254 patients. The patients were divided into 2 groups as symptomatic (115 patients) and asymptomatic (139 patients) patients. The study was approved by the ethics committee of our institution. Patients who had 50%-70% stenosis in the carotid artery were included in the study and those with any other condition (such as atrial fibrillation) that would lead to stroke/transient ischemic attack were excluded. All patients initially underwent carotid artery Doppler ultrasonography (CDUS), followed by computed tomography angiography (CTA). All patients were evaluated by a committee consisting of a neurologist, a cardiologist, a radiologist, and a cardiothoracic surgeon. Symptomatic patients were defined as those who had a history of ischemic cerebrovascular event with or without sequela, transient ischemic attack, or amaurosis fugax in the last 6 months. Patients who had become symptomatic within the last 1 month were excluded from the study. Patients with diabetes mellitus (DM) were included in the study after their blood glucose levels were regulated. Patients were included in the study at least 2 months after initiation of antiaggregant, antihyperlipidemic, and antihypertensive therapies. Blood samples were obtained from patients within an interval of 15 days. Laboratory parameters that have been analyzed in this study represent the mean value of 2 measurements taken at different time points by using the same device. The study exclusion criteria included a history of cranial hemorrhage, systemic inflammatory disease, cancer, acute coronary syndrome, previous myocardial infarction, heart failure, serious valve disease, renal and hepatic failure, hematologic disease, a body temperature of 37.0°C or higher, presence of an active infection, a white blood cell (WBC) count higher than 12.000 cells/μL, and the use of anti-inflammatory drugs or antibiotics.

Blood Samples

Fasting blood samples were drawn from a large antecubital vein of each patient for the determination of biochemical and hemostatic parameters. Tubes with EDTA were used for automatic blood count. The blood counts were obtained by a Beckman Coulter LH 780 Hematology Analyzer (Beckman Coulter, Inc., Brea, CA, USA). Total cholesterol, low-density lipoprotein, triglyceride, and high-density lipoprotein levels were measured by the colorimetric method (Abbott Laboratories, Abbott Park, IL, USA). Baseline NLR was calculated by dividing neutrophil count to lymphocyte count.

Definitions

Hypertension (HT) was defined as a systolic blood pressure of 140 mmHg and above or a diastolic blood pressure of 90 mmHg and above, or usage of antihypertensive drugs. DM was defined as a fasting blood glucose level of 126 mg/dL and above or current usage of oral antidiabetic drugs or insulin. All patients who smoked regularly were considered smokers. Hyperlipidemia (HPL) was defined as a total cholesterol level of 200 mg/dL or above. Coronary artery disease was defined angiographically as the presence of a plaque resulting in 50% or more stenosis in a major coronary artery. The body mass index was calculated by dividing body weight (kg) by the square of the height (m).

Doppler Ultrasonography and CTA Assessments

Carotid artery stenosis was first evaluated by CDUS and then by CTA. CDUS examination was performed using the Esaote SpA MyLabClass C (Esaote SpA, Florence, Italy) device with the linear array probe, which allows selection of frequencies between 3 and 11 mHz. CTA examination was performed using the Philips Brilliance 64 detector CT (Holland) device (Philips Healthcare, 5680