Persistent Leukocytosis—Is this a Persistent Problem for Patients with Acute Ischemic Stroke?

Amelia K. Boehme, MSPH,*† Andre D. Kumar, MD,‡ Michael J. Lyerly, MD,†
Michael A. Gillette, MSPH,‡ James E. Siegler, MD,‡ Karen C. Albright, DO, MPH,*†§||
T. Mark Beasley, PhD,¶ and Sheryl Martin-Schild, MD, PhD‡

Background: In the setting of acute ischemic stroke (AIS), leukocytosis has been shown to be an indicator of inflammatory response. Although leukocytosis on admission has been shown to correlate with initial stroke severity in AIS patients, no work has been done to assess if there are differences in transient or persistent leukocytosis in patients without infection. The objective of this study is to determine the clinical significance of persistent versus transient leukocytosis during the early phase of AIS. *Methods:* Patients who presented with AIS to our center within 48 hours of symptom onset between July 2008 and June 2010 were retrospectively identified by chart review. Patients were included if they had leukocytosis on admission (defined as white blood cell count $>11,000/\mu L$ based on laboratory reference range values). A logistic regression model was used to evaluate persistent leukocytosis (leukocytosis 48 hours after admission) as a predictor of several outcome measures, including good functional outcome (discharge modified Rankin Scale score of 0-2). Marginal effects were used to estimate the probability of poor functional outcome. *Results:* Of the 438 patients screened, 49 had leukocytosis on admission and of those 24 (49%) had persistent leukocytosis. NIHSS score correlated significantly with persistence of leukocytosis ($r = .306$; $P = .0044$). More people with transient leukocytosis (leukocytosis lasting <48 hours) had a good functional outcome (44% versus 16%; $P = .006$). After adjusting for baseline NIHSS score, persistent leukocytosis was not a significant independent predictor of good functional outcome, but showed an association (OR, 2.5; 95% CI, .562-10.7; $P = .2322$). Persistent leukocytosis after adjusting for age and NIHSS score at admission is associated with a poor functional outcome, but it is not statistically significant (OR, 2.43; 95% CI, .59-9.87; $P = .2151$). After controlling for age and NIHSS score on admission, for patients with persistent leukocytosis, the probability of having poor functional outcome at discharge was increased by 16 percentage points. *Conclusions:* Persistent leukocytosis is associated with higher baseline NIHSS scores. Persistent leukocytosis is tightly linked with baseline stroke severity and is associated with poor patient

outcomes. Our study found that patients with persistent leukocytosis are more likely to present with severe strokes and maintain a high NIHSS score at 24 hours after admission, unlike patients without leukocytosis or patients with transient leukocytosis. Furthermore, it appears that persistent leukocytosis outside the setting of an infection negatively impacts the short-term functional outcome of AIS patients. Identifying patients with persistent leukocytosis could help to prognosticate and target patients that may benefit from future anti-inflammatory interventions. **Key Words:** Leukocyte—ischemic stroke—stroke care—inflammation.

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Introduction

In the setting of acute ischemic stroke (AIS), leukocytosis has been shown to be an indicator of inflammatory response.[1,2] Although leukocytosis on admission has been shown to correlate with initial stroke severity in AIS patients, no work has been done to assess if there are differences in transient or persistent leukocytosis in patients without infection.[3,4] In patients who experience neurologic deterioration after AIS, concurrent leukocytosis appears to correlate with poor functional outcomes.[5] Akopov et al found an association between leukocytosis during the acute period and poor neurologic outcomes,[6] but other data suggest that may have been simply an acute stress reaction with little to no impact on outcome.[7,8] Additionally, leukocytosis has been shown to be predictive of in-hospital strokes indicating a close relationship between leukocytosis and stroke.[8,9] This leukocytosis event may only be transient in some patients, however. The primary objective of this study was to compare AIS patients who presented without leukocytosis with patients who presented with transient and persistent leukocytosis. The secondary objective was to assess the relationship of these groups with stroke severity on presentation and short-term functional outcomes.

Methods

Study Population and Variable Definition

Patients with AIS who presented to our center between July 2008 and June 2010 were retrospectively identified. Patients were excluded if they were admitted more than 48 hours after last seen normal, had an unknown last seen normal time, experienced an in-hospital stroke, received steroids in the month before admission, or had a documented infection 72 hours before or after admission. Standard infection definitions were used.[5] Patients with underlying hematologic disorders were excluded. Leukocytosis was defined as white blood cell count greater than 11,000/μL based on laboratory reference range values. Outcomes include modified Rankin Scale (mRS) score at discharge, symptomatic intracerebral hemorrhage (sICH), and favorable discharge disposition. sICH was defined as a type 2 parenchymal hemorrhage with deterioration in National Institutes of Health

Stroke Scale (NIHSS) score of 4 or more points or death.[10] Favorable discharge disposition was defined as discharge home or to an inpatient rehabilitation center.[11] Baseline characteristics were compared among AIS patients with persistent leukocytosis, transient leukocytosis, and no leukocytosis. Persistent leukocytosis was defined as patients who had leukocytosis for greater than 48 hours. Transient leukocytosis was defined as patients who had leukocytosis, but for less than 48 hours.

Statistics

Continuous variables were evaluated using the mean ± SD or median with range for non-normal distributions and median tests. Categorical variables were assessed using the chi-square tests or Fisher exact test, whichever appropriate. The Spearman correlation was used to assess the relationship between stroke severity, as measured by NIHSS, and each leukocytosis group. Logistic regression models were used to assess the relationship between leukocytosis and poor functional outcome, as measured by an mRS score of 3-6. Marginal effects were used to estimate the probability of poor functional outcome.

Results

Of the 292 patients who met inclusion criteria, 49 (16.8%) presented with leukocytosis on admission. Patients with leukocytosis on admission were similar in age, gender, and race when compared with patients without leukocytosis on admission (Table 1). Clinically, patients with leukocytosis presented with more severe strokes (median NIHSS score 9 versus 5; $P = .0026$; Table 1) when compared with nonleukocytosis patients.

Of the 49 patients presenting with leukocytosis, 24 (49%) had persistent leukocytosis. Age, gender, and race were similar between groups; however, the median NIHSS on admission (Figure 1) score in patients with persistently elevated leukocytosis was twice that of patients with transient leukocytosis (14 versus 7; $P = .0476$; Table 2). NIHSS score at 24 hours remains higher in the persistent group (12 versus 3; $P = .0590$). There was no statistically significant difference in the median change in NIHSS score from baseline to 24 hours among groups.