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

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Abstract

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/ μ 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

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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.

Keywords

Leukocyte; ischemic stroke; stroke care; inflammation

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/ μ L 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 $\pm$ 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.

Patients with transient and persistent leukocytosis did not differ with respect to favorable discharge disposition (discharge home or to an inpatient rehabilitation) or sICH (Table 3). Compared with patients with transient leukocytosis, those with persistent leukocytosis beyond 48 hours had longer lengths of stay on average (10.4 versus 6.6 days; $P = .044$). Fewer patients with persistent leukocytosis were able to achieve a favorable functional outcome (mRS score of 0-2) at the time of discharge (16% versus 44%; $P = .006$). NIHSS score significantly correlated with the persistence of leukocytosis ($r = .306$; $P = .0044$). Although stroke severity correlated with persistent leukocytosis, it did not correlate with transient leukocytosis. The crude model assessing persistent leukocytosis as a predictor of

poor outcome shows a significant association (OR, 3.26; 95% CI, 1.06-9.89; $P = .0386$). After adjusting for NIHSS score, persistent leukocytosis was no longer an independent, significant predictor of good functional outcome (OR, 2.5; 95% CI, .562-10.7; $P = .2322$). A similar relationship was seen when adjusting for age and NIHSS score on admission (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. A similar relationship between transient leukocytosis and poor functional outcome was not observed (OR, .99; 95% CI, .34-2.90; $P = .9950$).

Discussion

In keeping with previous studies, our study found that nearly 1 in 5 AIS patients had leukocytosis on admission with more than half of these patients experiencing persistent leukocytosis. Interestingly, a longer duration of leukocytosis appeared to be associated with higher stroke scale scores on admission. In addition to having more severe strokes on admission, patients with persistent leukocytosis had higher NIHSS scores at 24 hours. Similar to what has been described in the trauma literature, we postulate that leukocyte activation in AIS may be, at least in part, because of an elevation in circulating catecholamine, cytokine, and cortisol levels.¹²⁻¹⁶ Previous stroke studies have demonstrated that patients with greater inflammation have larger volumes of injured tissue where leukocytes can accumulate leading to further postischemic injury.^{6,8,17} Therefore, persistence of leukocytosis can ultimately lead to worse neurologic outcomes. Although our sample size was small and the result was not statistically significant, we observed an association between persistent leukocytosis and poor outcomes that was not seen with temporary leukocytosis. The crude association was statistically significant, whereas the addition of the confounder NIHSS score explained some of the association as seen by the lowering of the odds ratio and the statistical nonsignificance. Despite the move from significant to nonsignificant there remained an association between persistent leukocytosis and poor functional outcome. Future studies in larger cohorts are needed to see if this association will be significant when the sample size is increased.

Leukocytosis is not an uncommon finding in AIS patients. Although it has been previously demonstrated that the presence of an elevated leukocyte count correlated with poor outcomes,^{5,6} the impact of the timing and duration of this leukocytosis has not been established. Our study demonstrates that patients with persistent leukocytosis, lasting more than 48 hours after admission, have longer hospitalizations and worse functional outcomes compared with patients with transient leukocytosis.

This study was designed to assess the effect of leukocytosis independent of coexisting infections and artificial or iatrogenic elevations in leukocyte levels. By excluding patients with clinical evidence of active infection, we were still able to demonstrate that a significant proportion of our AIS patients present with leukocytosis. Infections of the respiratory and urinary tracts complicate AIS in up to 30% of cases and may potentiate mental status changes and worsen stroke symptoms,¹⁸ possibly in a manner independent of leukocytosis. Furthermore, previous studies have shown that an infection before hospitalization is

associated with stroke severity,¹⁹ so by excluding patients with clinical evidence of infections we are able to truly assess the relationship between leukocytosis and stroke severity. As we have demonstrated, leukocytosis lasting more than 48 hours in the absence of infection may contribute to worsening outcomes in this population, or at least serve to confirm the clinical severity of infarct. The tight association between the NIHSS score and persistent leukocytosis has explained some of the association between persistent leukocytosis and poor outcomes, but the increased probability of having poor functional outcomes for patients with persistent leukocytosis after adjusting for age and NIHSS score remains.

Our study is not without limitations. Our sample was derived from a single tertiary care hospital. Our analysis is retrospective and our outcomes are short term. Our limited sample size may have prevented us from detecting existing differences between groups leading to an inability to detect statistical significance where the odds ratios indicate there is an association.

Conclusions

Despite its limitations, this is the first study to examine prolonged leukocytosis in AIS patients. 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.

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Figure 1. Boxplot of the baseline NIHSS score for the 3 groups of leukocytosis ($P = .0024$). Abbreviation: NIHSS, National Institutes of Health Stroke Scale.

Table 1

Comparison of patients with leukocytosis on admission with patients without leukocytosis on admission

Variables	Leukocytosis (n = 49)	No leukocytosis (n = 243)	P value
Age, median, y (range)	59 (19-86)	65 (22-96)	.2853
Black race, %	24 (48.9%)	167 (68.7%)	.0546
Male, %	23 (46.9%)	146 (60.1%)	.0892
NIHSS score at baseline, median (range)	9 (1-31)	5 (0-28)	.0100
NIHSS score at 24 h, median (range)	7 (0-32)	4 (0-37)	.3830
Change in NIHSS score	-1 (-8 to 4)	-1 (-14 to 37)	.565
Glucose on admission, median mg/dL (range)	135 (79-569)	118 (76-625)	.0770
Intravenous tissue plasminogen activator, %	17 (34.7%)	68 (27.9%)	.3455
History of hypertension, %	33 (68.7%)	182 (75.2%)	.3507
History of diabetes, %	17 (34.7%)	87 (35.9%)	.8671
History of dyslipidemia, %	22 (45.8%)	107 (44.4%)	.8551
TOAST, %			.0552
Cardioembolic	11 (27.5%)	50 (25.7%)	
Large vessel	9 (22.5%)	48 (24.7%)	
Small vessel	4 (10.0%)	48 (24.7%)	
Cryptogenic, >1 cause	13 (32.5%)	32 (16.5%)	
Cryptogenic, no cause found	1 (2.5%)	8 (4.1%)	
Other	2 (5.0%)	8 (4.1%)	

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in acute stroke treatment.

Table 2

Comparison of baseline characteristics in patients with persistent leukocytosis versus patients with resolved leukocytosis

Variables	Persistent leukocytosis (n = 24)	Transient leukocytosis (n = 25)	P value
Age, median, y (range)	66 (19-85)	59 (31-86)	.7716
Black race, %	11 (45.8%)	13 (52.0%)	.5185
Male, %	12 (50.0%)	14 (56.0%)	.6740
NIHSS score at baseline, median (range)	14 (1-31)	7 (1-25)	.1180
NIHSS score at 24 h, median (range)	12 (0-32)	3 (0-26)	.0590
Change in NIHSS score from admission to 24 h	-1 (-8 to 4)	-1 (-6 to 4)	.6740
Glucose on admission, median mg/dL (range)	136 (79-569)	134 (85-304)	.7039
Intravenous tissue plasminogen activator, %	8 (33.3%)	9 (36.0 %)	.8446
History of hypertension, %	15 (62.5%)	15 (62.5%)	.3502
History of diabetes, %	8 (33.3%)	9 (36.0%)	.8446
History of dyslipidemia, %	8 (33.3%)	14 (58.3%)	.0822
TOAST, %			.3190
Cardioembolic	8 (36.4%)	3 (16.7%)	
Large vessel	3 (13.6%)	6 (33.3%)	
Small vessel	1 (4.6%)	3 (16.7%)	
Cryptogenic, >1 cause	7 (31.8%)	6 (33.3%)	
Cryptogenic, no cause found	1 (4.6%)	0	
Other	2 (9.1%)	0	

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in acute stroke treatment.

Table 3

Outcome characteristics

Variables	Leukocytosis persists at 48 h after admission (n = 24)	Leukocytosis resolved by 48 h after admission (n = 25)	P value
mRS score on discharge, median (range)	4 (0-5)	3 (0-5)	.2112
mRS score 0%-2%	6 (16%)	17 (44%)	.006
LOS, mean (SD)	10.4 (6.8)	6.6 (6.1)	.044
Favorable discharge, %	29 (74%)	32 (84%)	.2868
sICH, %	1 (2.2%)	1 (2.4%)	.7698

Abbreviations: LOS, length of stay; mRS, modified Rankin Scale; SD, standard deviation.