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Total and differential leukocyte counts in ischemic stroke caused by vertebrobasilar artery dissection

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ABSTRACT

Introduction: Vertebrobasilar artery dissection(VBD) is a common etiology of posterior circulation stroke(PCS). However, the etiology of VBD itself remains unclear. The present study aimed to test whether inflammation is involved in the mechanism of VBD by evaluating its relationship with total and differential leukocyte counts.
Methods: Patients with PCS caused by VBD or by large artery atherosclerosis(LAA) were recruited between January 1, 2012 and December 31, 2014 from the Taipei Veterans General Hospital. Age- and sex-matched non-stroke(NS) volunteers were also included. Univariate and multivariate analyses were performed to compare total/differential leukocyte counts among VBD, LAA, and NS groups.
Results: One-hundred-one patients with VBD [average age: 64.8(15.1) years; 77(76.2%) males], 70 with LAA [average age: 73.9(10.6) years; 44(62.9%) males], and 202 NS [average age: 64.8(15.1) years; 77(76.2%) males] patients were included in the present study. Compared with the NS and LAA groups, respectively, the VBD group had significantly higher total leukocyte and neutrophil counts and frequency of high leukocyte ($> 10,000 \times 10^6$/L) and high neutrophil ($> 8000 \times 10^6$/L) counts. Multivariate analyses, adjusted for age, sex, and vascular risk factors, showed that the VBD group, compared with the other groups, had an odds-ratio of 5.04 (95% confidence interval:2.43–10.43) and 5.90 (2.70–12.92) with respect to the prevalence of high leukocyte and high neutrophil counts.
Conclusion: VBD was associated with high leukocyte and neutrophil counts. Our results support that inflammation and neutrophil-related pathophysiology might be involved in the mechanism of VBD; however, the causal relationship would need further investigations.

1. Introduction

Arterial dissection implies a tear in the arterial wall, intima, or connective tissue in the media, leading to the intrusion of blood within the layers of the arterial wall (intramural hematoma); this causes stenosis of the lumen when blood collects between the intima and media and might result in thrombus formation at the lesion [1]. Magnetic resonance imaging (MRI) has been proven as a sensitive tool for the diagnosis of cervicocephalic artery dissection owing to its high-resolution imaging and direct visualization of the intramural hematoma [2]. Vertebrobasilar artery dissection (VBD) is characterized by the intrusion of blood within the vascular layers (intramural hematoma) in the vertebral artery (VA) and/or the basilar artery (BA) on images [1]. With the popularity of MRI use in acute ischemic stroke, intracranial VBD has been increasingly recognized as the etiology of posterior circulation ischemic stroke (PCS) [3–5]. We recently reported that PCS is a heterogeneous disease, and one-fourth of all instances of PCS are caused by intracranial VBD [5]. Intracranial VBD-related PCS usually occurs in younger adults, but its short-term outcome or mortality rate is not always favorable [1,6]. Nevertheless, the etiology of VBD remains unclear. Heritable connective tissue diseases with underlying structural defects of the arterial wall could only be identified in 1–5% of cases with cervicocephalic artery dissection; trauma or precipitating events, which injure the arterial wall, are also associated with VBD, but are not able to account for all of the cases either [7].

A recent respiratory tract infection has been reported to be a risk factor for cervical artery dissection [7,8]. In addition, inflammation is known to be involved in several vascular diseases [9] and leukocyte infiltration has been demonstrated in aortic dissection as well [10,11]. We therefore hypothesized that inflammation, which could be triggered

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by infection or other factors, might play a role in the etiology of VBD. To validate this hypothesis, we analyzed the total and differential leukocyte counts, simple and widely used markers of inflammation, in patients with VBD-related PCS. Since leukocytes have been shown to be elevated in acute ischemic stroke, especially in cases with atherosclerotic origins [12–15], to avoid the confounding effect of ischemic stroke itself, we also included patients with large artery atherosclerosis (LAA)-related PCS in addition to age- and sex-matched normal controls for comparisons.

2. Materials and methods

2.1. Study population

Since 2009, Taipei Veterans General Hospital Stroke Registry has collected data for all patients with acute stroke admitted to the emergency room or Neurology Department wards. Patient data were reviewed and a consensus concerning their stroke etiologies was reached by both neurologists and radiologists. All patients have brain MRI and MRA examinations. No subjects had digital subtraction angiography performed. The following standardized criteria were used to classify stroke etiology in VBD and LAA [5,16]:

(1) VBD. Vascular studies showed (a) occlusion or severe stenosis (> 50%) of the VA and/or BA; (b) gradually tapered and/or long-segmental narrowing of the stenotic/occlusive vessel; (c) intramural hematoma, intimal flap, or double lumen by high-resolution or standard MRI T1 sequence; and (d) other characteristics of arterial dissection including positive vascular remodeling (vascular dilatation), associated aneurysm, eccentric hematoma, long segmental wall thickening (intima tearing), unusual location of atherosclerotic plaque and serial changes (rapidly recovered or progressed stenosis). In cases of uncertain diagnosis, particularly in patients with associated atherosclerosis, we would do high resolution (3 mm slice) MR scan over stenotic area and looked at characteristics of vessel walls favoring VBD. The detailed protocol of high resolution MRI was as followed: Axial T1, T2 & contrast-enhanced T1; Slice thickness = 3 mm, NEX = 6 (T2) & 4 (T1), FOV = 13x13cm, matrix = 288 × 224 (T2) & 288 × 192 (T1); fat suppression; double inversion recovery images.

(2) LAA. Vascular studies showed occlusion or severe stenosis (> 50%) of the VA and/or BA. There should be multiple or diffusely atherosclerotic changes in the other large arteries. An abrupt cut-off of vessels was considered to more likely be due to embolism and was not considered for this category.

The present study recruited patients with VBD or LAA who were registered in the stroke registry between January 1, 2012 and December 31, 2014. Patients with (1) autoimmune diseases, (2) hematological diseases, or (3) simultaneous acute cerebral infarcts in the territory of anterior circulation were excluded. Non-stroke individuals (NS) were volunteers who were age- and sex-matched to patients of VBD. All participants provided informed consent. The Institutional Review Board of the Taipei Veterans General Hospital approved the present study.The I-Lan Longitudinal Aging Study is a community-based aging cohort study in the I-Lan County of Taiwan that aimed to evaluate the interrelationship between the geriatric syndromes and brain structural abnormalities [15]. In brief, community-dwelling adults aged 50 years or older from Yuanshan Township in I-Lan County were invited to participate in the study through household registrations organized by the government. The inclusion criteria of the I-Lan Longitudinal Aging Study were: (1) inhabitants of I-Lan County who did not intend to move in the near future, and (2) aged 50 years or older. Any subject that met any one of the following conditions was excluded from the study: (1) unable to communicate and complete an interview, (2) unable to complete a simple motor task (e.g., a 6-m walk) due to functional disability, (3) suffering from any major illness with limited life expectancy (< 6 months in general), (4) having any contraindication to an MRI such as metal implants, (5) having been institutionalized for any reason and (6) having known neuropsychiatric diseases such as dementia, stroke, brain tumor, or major depression. The whole study was approved by the Institutional Review Board of the National Yang Ming University, Taipei, Taiwan. All the participants provided informed consent.

2.2. Vascular risk factors determination

Vascular risks factors were assessed by self-report and/or by measurement. Hypertension was defined as a self-report of a current anti-hypertensive medication prescription or as a measurement of systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg. Diabetes mellitus (DM) was defined as a self-report of current DM treatment or a measurement of HgbA1c ≥6.5%. Hyperlipidemia was recorded if there was a self-report of the use of statins or a blood level of total cholesterol ≥240 mg/dL.

2.3. Leukocyte counts assessment

Patient blood samples analyzed in this study were collected in Emergent Department within 1–12 h of symptom onset. Total and differential leukocyte counts were performed with an automated analyzer (LH 780 Hematology Analyzer, Beckman Coulter, Brea, CA USA) for all subjects.

2.4. Statistical analysis

Analyses were performed with SAS software, version 9.1 (SAS Institute, Cary, NC USA). All values were expressed as mean (± SD) for continuous variables and number (percentages) for discrete variables. Group comparisons were made using nonparametric Mann-Whitney *U* tests (non-normalized data). The χ^2 test or Fisher's exact test was performed for categorical variables, as appropriate. Univariate and multivariate regression analyses with direct leukocyte counts or the presence of high leukocyte counts as a dependent variable were performed to test the relationship between leukocyte and VBD. High leukocyte counts were defined as leukocyte counts > 10,000 × 10^6/L, neutrophil counts > 8000 × 10^6/L (> 10,000 × 80%), or monocyte counts > 900 × 10^6/L (> 10,000 × 9%). We adjusted for other independent variables including age, sex, vascular risk factors (hypertension, DM, hyperlipidemia, and cigarette smoking) or admission NIH stroke scale (stroke severity, NIHSS). All statistically significant levels were defined as $P < .05$.

3. Results

There were 101 VBD, 70 LAA, and 202 NS included in the present study. Only two patients with VBD had an extracranial (cervical) VA dissection; the others were intracranial VA and/or BA dissection. Baseline characteristics are shown in Table 1. Compared with the age- and sex-matched NS group, the VBD group had more vascular risk factors. The VBD group were significantly younger and included more males and more frequent cigarette smoking as compared with the LAA group. Stroke severity between the VBD and LAA groups were similar.

The distribution of total leukocyte and differential counts are shown in Fig. 1. Compared with the NS group, the VBD group had significantly higher leukocyte, neutrophil, and monocyte counts and lower lymphocyte counts; in contrast, compared with the LAA group, the VBD group had significantly higher leukocyte and neutrophil counts independent of age, sex and stroke severity (Table 1). The prevalence of high total leukocyte and differential counts are also shown in Table 1 and Fig. 1. There were more subjects with high leukocyte and neutrophil counts in the VBD group compared with the NS and LAA groups,

Table 1
Comparisons between vertebrobasilar artery dissection group and non-stroke group and large artery atherosclerosis group respectively.

	VBD (*n* = 101)	LAA (*n* = 70)	NS (*n* = 202)	*p*[*]	*p*[†]
Age, years, mean (SD)	64.8 (15.1)	73.9 (10.6)	64.8 (15.1)	–	< 0.001
Sex, men, n (%)	77 (76.2)	44 (62.9)	154 (76.2)	–	0.063
Vascular risk factors, n (%)					
Hypertension	80 (80.0)	62 (88.6)	87 (43.1)	< 0.001	0.149
Diabetes mellitus	51 (51.0)	34 (48.6)	35 (17.3)	< 0.001	0.876
Hyperlipidemia	34 (34.0)	27 (38.6)	14 (6.9)	< 0.001	0.626
Cigarette smoking	31 (31.0)	11 (15.7)	50 (24.8)	< 0.001	0.052
NIH Stroke Scale, score, mean (SD)	7.0 (8.0)	6.4 (7.5)	–	–	0.057
					p[‡]
Cell count, X10^6/L, mean (SD)					
Total Leukocyte	9043.4 (3245.1)	8102.3 (3102.8)	6009.3 (1489.2)	< 0.001	0.007
Neutrophil	6685.3 (3277.4)	5601.6 (2600.6)	3522.5 (1125.2)	< 0.001	0.012
Lymphocyte	1720.3 (726.0)	1628.5 (732.6)	1902.6 (551.0)	0.008	0.364
Monocyte	569.5 (227.4)	509.9 (230.6)	399.3 (126.8)	< 0.001	0.132
High leukocyte (> 10,000), n (%)	29 (28.7%)	13 (18.6%)	2 (1.0%)	< 0.001	0.047
High Neutrophil (> 8000), n (%)	27 (26.7%)	10 (14.3%)	2 (1.0%)	< 0.001	0.042
High Monocyte (> 900), n (%)	9 (8.9%)	3 (4.3%)	0	0.995	0.233

VBD, vertebrobasilar artery dissection; LAA, large artery atherosclerosis; NS, non-stroke.
[*] Nonparametric Mann Whitney tests comparisons between VBD and NS groups.
[†] Nonparametric Mann Whitney test comparisons between VBD and LAA groups.
[‡] Multivariate regression analyses adjusted for age, sex and stroke severity with direct leukocyte counts or the presence of high leukocyte counts as a dependent variable and VBD/LAA as one of the independent variables.

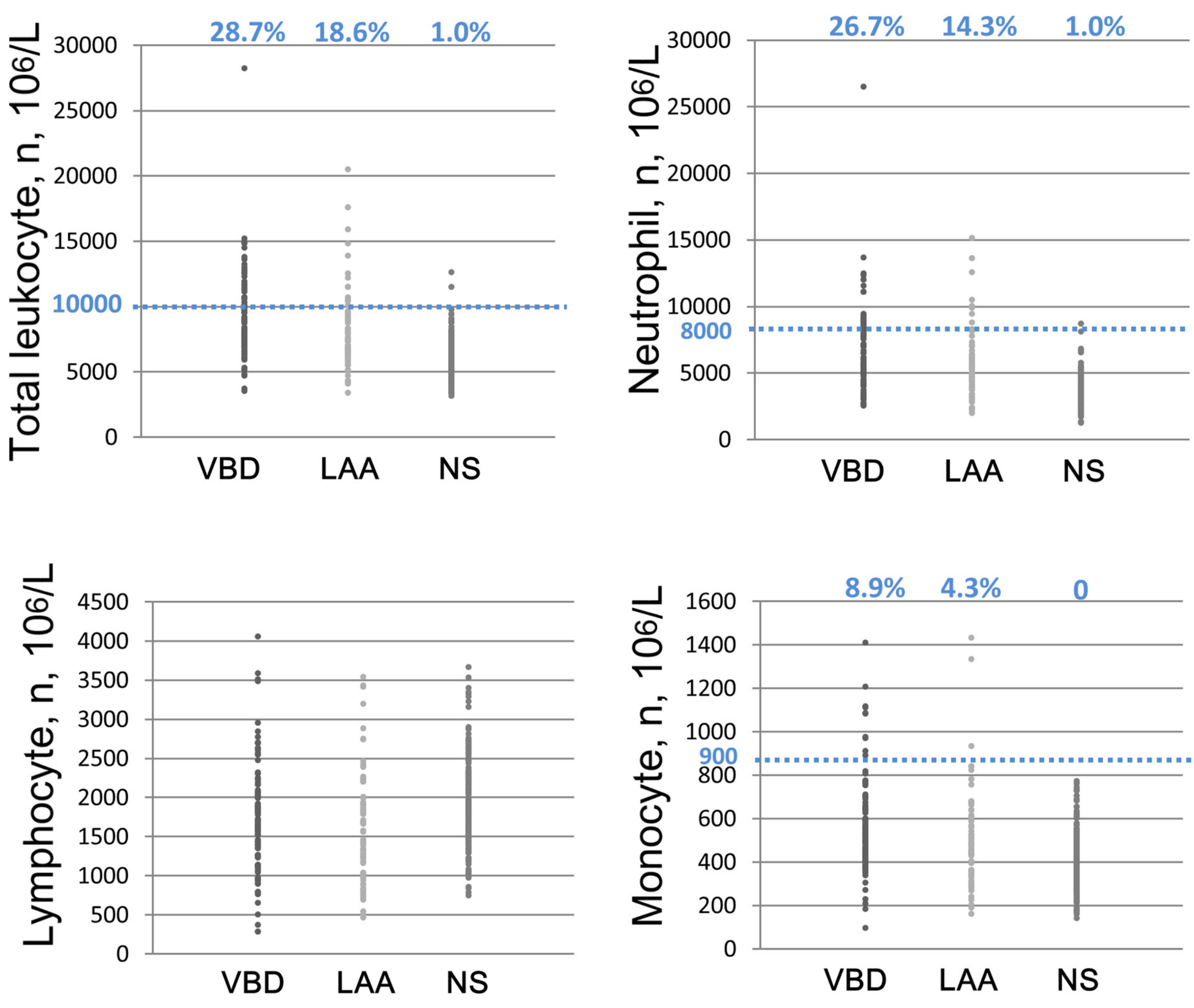

Fig. 1. Distributions of total and differential leukocyte counts in each group.
Percentage of high leukocyte, neutrophil and lymphocyte counts (blue numbers) in each group are demonstrated above the scattered plots. VBD, vertebrobasilar artery dissection; LAA, large artery atherosclerosis; NS, non-stroke. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Multivariate analyses of the associations between high leukocyte/neutrophil counts and vertebrobasilar artery dissection.

	Odds-ratio	95% confidence interval	p
Total leukocyte counts > 10,000			
VBD versus NS and LAA			
Model 1	6.76	3.42–13.37	< 0.001
Model 2	5.04	2.43–10.43	< 0.001
Neutrophil counts > 8000			
VBD versus NA and LAA			
Model 1	8.21	3.94–17.11	< 0.001
Model 2	5.90	2.70–12.92	< 0.001

VBD, vertebrobasilar artery dissection; LAA, large artery atherosclerosis; NS, non-stroke. Model 1, adjusted for age and sex.
Model 2, adjusted for age, sex and vascular risk factors (hypertension, diabetes mellitus, cigarette smoking and hyperlipidemia).

respectively.

We then performed multivariate analyses adjusting for age, sex, and vascular risk factors to evaluate whether VBD was independently associated with high leukocyte and neutrophil counts (Table 2). The results showed that the VBD group, compared with the NS and LAA groups, had an odds-ratio (OR) of 5.04 (95% confidence interval: 2.43–10.43) and 5.90 (2.70–12.92) possessing high leukocyte and high neutrophil counts, respectively (Table 2). To eliminate the effect of ischemic stroke itself on leukocyte counts, we also did multivariate analyses comparing between VBD and LAA groups adjusting for age, sex, stroke severity (NIHSS) and vascular risk factors. The results showed that the significance was eliminated though the trend of difference was still in the same direction (Table 3).

4. Discussion

The present study has found an association between VBD and increased leukocyte counts, especially the neutrophils; about one-fourth of the patients with VBD-related PCS had high leukocyte and neutrophil counts.

Leukocyte count is reportedly associated with the presence and severity of ischemic stroke as well as systemic atherosclerosis [12–15,17]. Our results, after adjusting for age, sex, and stroke severity, still showed that PCS patients with VBD had more total leukocyte and neutrophil counts than patients with PCS caused by atherosclerosis. The significant relation between VBD and increased leukocyte counts was independent of age, sex, the presence of stroke and stroke severity. Multivariate analyses adjusting for age, sex, and vascular risk factors also showed a significantly higher prevalence of high leukocyte and neutrophil counts in VBD-related PCS than LAA-related PCS and normal controls. Notably, the blood samples that were analyzed were taken within 1–12 h after onset of stroke, which minimized the possible effect of post-stroke infections or stroke-induced immunosuppression on leukocyte counts.

Table 3
Multivariate analyses of the associations between high leukocyte/neutrophil counts and vertebrobasilar artery dissection (versus large artery atherosclerosis).

	Odds-ratio	95% confidence interval	p
Total leukocyte counts > 10,000			
VBD versus LAA	1.44	0.63–3.29	0.383
Neutrophil counts > 8000			
VBD versus LAA	1.71	0.70–4.18	0.239

VBD, vertebrobasilar artery dissection; LAA, large artery atherosclerosis.
Model adjusted for age, sex, stroke severity and vascular risk factors (hypertension, diabetes mellitus, cigarette smoking and hyperlipidemia).

As with racial differences in the location of atherosclerotic lesions which can cause stroke [18], cervicocephalic arterial dissection also occurs mostly intracranially in Asian populations (intracranial artery dissection accounts for 68–98% of cervicocephalic arterial dissection) while the Western populations have more extracranial arterial dissection [1,19–22]. Most of the previous studies about the relationship between inflammation and cervicocephalic arterial dissection were focusing on cervical arterial dissection instead of intracranial arterial dissection [24,25]. Case-control studies have shown that patients with spontaneous cervical artery dissection including VA dissection have more frequently a recent episode of infection in the preceding days [23]. The same study group later found that cervical artery dissection is associated with a higher leukocyte count [24]. Imaging studies have also revealed signs of local inflammation around the affected vessels of patients with spontaneous cervical arterial dissection [25,26]. It is uncertain whether the mechanisms of intracranial arterial dissection and cervical (extracranial) arterial dissection are similar. The results of the present study included 98% of patients having intracranial arterial dissections suggest that inflammation might also be involved in the pathophysiology of intracranial VBD.

In the present study, higher leukocyte counts in patients with VBD were mainly contributed by higher neutrophil counts. Circulation neutrophils may infiltrate the vascular wall and release vasoactive or cytotoxic mediators including several proteolytic enzymes and then initiate or potentiate the disintegration of the arterial wall [10,11,27]. Correspondingly, animal and human studies have shown the involvement of neutrophils and their release of matrix metalloproteinases in the mechanism of aortic dissection; and neutrophil depletion in animal models significantly decreases the incidence of aortic dissection [10,11]. We postulated that this neutrophil-related mechanism might also account for VBD. Since the vertebrobasilar system has a lower flow than the carotid system, circulatory activated neutrophils might have a higher chance of slowly rolling along the endothelium of vertebrobasilar arteries and activating an inflammatory process there [28]. Our postulation may explain a higher incidence of arterial dissection in the vertebrobasilar system than the carotid system [3].

Our results also revealed that the strength of the association of leukocyte count was stronger with VBD versus NS than VBD versus LAA groups. The significance of increased leukocyte counts in VBD group was diminished when compared with LAA group (Tables 1 & 3). To avoid the effect of stroke itself and exaggerated effect of atherosclerosis on leukocytes, we would need a larger population of VBD without stroke to elucidate the sole effect of VBD on leukocyte counts.

There are several potential limitations of this study. First, we did not have reliable data on clinical infection history and thus were unable to make statements about the underlying causes of the elevated leukocyte counts. Secondly, we only evaluated patients of VBD with PCS. It is uncertain whether the associations with leukocytes could also be applied to VBD without stroke. Thirdly, the other inflammatory markers or leukocyte-related mediators which may provide further mechanistic insights were not evaluated in the present study. Finally, the cross-sectional design could not identify causal relationships between increased leukocyte counts and VBD. Arterial dissections and associated brain infarction in our cases involve injury to the arterial wall and brain tissue which could also trigger inflammation. Thus, the association of inflammation with dissection could also readily be explained by a reaction to the vessel wall injury rather than a causative factor in the dissection. A longitudinal study with a larger population and investigations of other inflammatory markers and leukocyte-related mediators is needed to validate our postulation about the mechanisms of VBD.

Declaration of Competing Interest

All authors report no conflict of interest.

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Author contributions

All authors have been involved in drafting the manuscript and revising it critically for important intellectual content and given final approval of the version to be published. We also confirm that each author have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conceptualization and design: CPC, FCC.

Acquisition of data: CPC, FCC, HCH, JYT.

Analysis and interpretation of data: CPC, WTC, FCC.

Manuscript drafting: WTC, CPC.

Statistical analyses: WTC, CPC.

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