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Clinical Short Communication

Radiological features and outcomes of essential thrombocythemia-related stroke

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ABSTRACT

Background: Essential thrombocythemia (ET) is known to be associated with an increased vascular event, but the stroke patterns and prognosis have not been studied.
Methods: Between January 2013 and December 2017, acute ischemic stroke patients with ET who were admitted to two tertiary hospital stroke centers in Seoul, Korea were included. We retrospectively reviewed their clinical, laboratory and imaging data. Stroke mechanism was determined as ET-only when no atherosclerotic, cardioembolic, or lacunar stroke etiology was demonstrated and as ET-plus group when any specific etiology was combined. Each group was analyzed to ascertain stroke patterns and outcomes.
Results: A total of 26 patients were included, and their mean age was 66 ± 17 years, including 12 female patients. There were 12 ET-only cases and 14 ET-plus cases per stroke mechanism. The ET-plus group included 7 large artery atherosclerosis, 5 small vessel occlusion, and 2 cardioembolic cases. Multiple scattered lesions involving multiple vascular territories were more prevalent in the ET-only group. Poor outcome (modified Rankin scale > 2 at discharge) was noted in 13 cases (50.0%), and old age, female sex, prior diagnosis of ET to stroke and low hemoglobin level were associated with poor outcome.
Conclusion: ET-related stroke displayed a characteristic infarction pattern, such as multiple embolisms.

1. Introduction

Ischemic stroke is one of the most dreadful thrombotic manifestations of essential thrombocythemia (ET), which is a myelodysplastic syndrome with abnormally increased platelet count not due to overt hematologic malignancy [1]. The major risk factors associated with clinical thrombosis among ET patients includes age > 60 years, Janus kinase 2 (JAK2) mutation, and previous thrombosis history [1]. There exist several case series about clinical manifestations and neurological outcome regarding stroke patients with ET [2–4]. However ischemic lesion pattern and neurological consequence after stroke had not been elucidated. We illustrated radiological characteristics of the stroke mechanism combined with ET, and tried to derive prognostic factors associated with poor functional outcome.

2. Methods

We retrospectively collected data of consecutive cerebral infarction patients who were diagnosed with ET from two university-based training hospitals (Chung-Ang University Hospital and Seoul National University Hospital) located in Seoul, Korea, between January 2013 and December 2017 after approval of Institutional Review Board of the two hospitals. The diagnosis of ET was confirmed by hematology specialist based on World Health Organization classification which consists of four major criteria: 1) sustained platelet count $\geq 450 \times 10^8$/L, 2) bone marrow biopsy revealing megakaryocyte proliferation, 3) not meeting criteria for other myeloid neoplasms, and 4) the presence of characteristic genetic mutations suggesting ET, together with one minor criterion including the presence of clonal marker or absence of evidence for reactive thrombosis [1]. When bone marrow biopsy was not possible, the preemptive diagnosis of ET was made when platelet count remained elevated for follow-up period without other specific cause of thrombocytosis. We excluded patients with premorbid functional disability measured as modified Rankins scale (mRS) 3 or more. Ischemic stroke was diagnosed when sudden onset focal neurological deficit was derived as a result of brain injury due to vascular etiology, which was documented by appropriate brain imaging. Neurological severity was measured on the National Institute of Health Stroke Scale (NIHSS) and mRS at discharge. Stroke mechanism was categorized into ET-only when a patient did not have any other discernable vascular risk factor/

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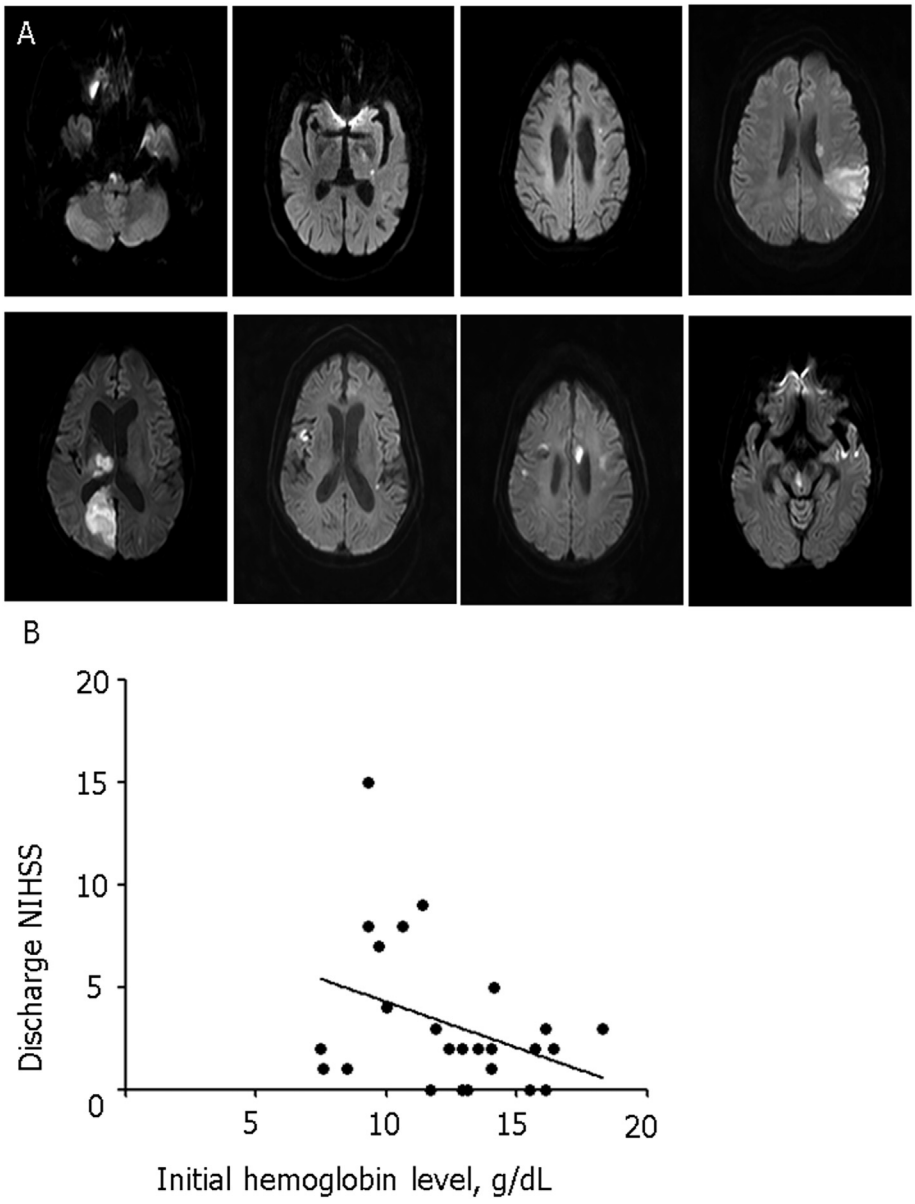

Fig. 1. The characteristics of cerebral infarction pattern with ET from brain diffusion weighted MR imaging.
The ET patients with conventional stroke etiology (ET-plus group) tend to present with infarction involving single vascular territory (A, upper panel). The first and second patient had small vessel occlusion types, the third patient with atherosclerotic stenosis of middle cerebral artery, and the fourth patient with atrial fibrillation. The patients with ET but without conventional stroke etiology (ET-only group) had widespread ischemic lesions extending single vascular territory (A, lower panel). The initial hemoglobin level tended to be inversely correlated with discharge neurological severity measured by the National Institute of Health Stroke Scale (B, Pearson's $r = -0.360$, $p = 0.07$).

pathology or embolic source explaining index stroke event, and ET-plus when traditional stroke etiologies, such as significant atherosclerotic stenosis, cardioembolism and small vessel occlusion defined as Trial of Org 10,172 in Acute Stroke Treatment criteria were combined [5]. To derive a prognostic factor, we compared demographic and laboratory variables between the patients with mRS 0–2 (good functional outcome) and those with mRS 3–6 (poor functional outcome). Categorical variables are presented with the number of patients and analyzed by Fischer's exact test or Pearson's chi-squared test and continuous variables presented with mean (standard deviation) and assessed by *t*-test.

3. Results

A total of 26 patients were included during the study period with 12 female patients (mean age: 66 ± 17 years). Stroke subtype included 12 ET-only cases and 14 ET-plus cases (7 large artery atherosclerosis, 5 small vessel occlusion, and two cardioembolic cases). Stroke patients due to ET-plus tends to have single lesions (Fig. 1A, upper panel), whereas embolic infarction pattern involving multiple vascular territory was more prevalent in ET-only group (Fig. 1A, lower panel; cases with multiple lesions: 8 out of 12 cases from ET-only group versus 4 out of 14 cases from ET-plus group, Pearson's chi-squared test, $p = 0.05$). For 14 ET-only stroke patients, 7 patients received dual antiplatelet agents, 3 patients were maintained with anticoagulation, one patient with aspirin, and one patient without any antithrombotic agent due to symptomatic hemorrhagic transformation. Five patients experienced neurological deterioration during index stroke, including two cases of symptomatic hemorrhagic transformation. Stroke recurrence was detected in seven patients during a median follow up of 25 months (interquartile range: 5, 44 months). The incidence of neurological deterioration (ET-only: 3 out of 12 cases, ET-plus: 2 out of 14 cases, Fischer's exact test, $p = 0.64$) and stroke recurrence (ET-only: 3 out of 12 cases, ET-plus: 4 out of 14 cases, log-rank test, $p = 0.99$) was not different between the two groups.

Comparison of clinical variables according to functional outcome at discharge revealed that old age, female sex, lower hemoglobin level and prior ET diagnosis are associated with poor neurological outcome (Table 1). Initial platelet count, JAK mutation status, preceding hydroxyurea/aspirin treatment and stroke mechanism were not associated neurological outcome. Correlation analysis between initial hemoglobin level and discharge NIHSS suggested inverse relationship (Pearson's $r = -0.360$, $p = 0.07$, Fig. 1B).

Table 1
Clinical and radiological characteristics between stroke patients with favorable outcome and those without favorable outcome.

	mRS 0–2	mRS 3–6	
Patient number	12	14	
Age, years, mean (SD)	58 (18)	74 (11)	0.02
Sex, female, n	1	11	0.01
Hypertension, n	5	8	0.24
Diabetes mellitus, n	5	5	0.99
Atrial fibrillation, n	0	2	0.48
Previous stroke, n	3	2	0.99
Initial NIHSS, mean (SD)	2.5 (1.5)	7.3 (6.4)	0.01
Discharge NIHSS, mean (SD)	1.1 (1.2)	5.2 (4.0)	0.003
ET only stroke mechanism, n	6	6	0.99
Systolic BP, mmHg, mean (SD)	142 (23)	149 (32)	0.52
White blood cell, $\times 10^9$/L, mean (SD)	12.8 (7.1)	13.2 (3.9)	0.90
Hemoglobin, g/dL, mean (SD)	14.2 (2.7)	10.9 (2.0)	0.002
Platelet, $\times 10^9$/L, mean (SD)	551 (65)	509 (105)	0.24
Total cholesterol, mg/dL, mean (SD)	171 (58)	152 (44)	0.37
LDL cholesterol, mg/dL, mean (SD)	104 (38)	93 (34)	0.45
Fasting glucose, mg/dL, mean (SD)	136 (70)	116 (48)	0.40
Anticoagulation, n	1	3	0.59
Dual antiplatelet agent, n	9	5	0.12
ET diagnosis before stroke, n	2	8	0.02
Bone marrow examination, n	5	8	0.24
JAK mutation, n	2	6	0.20
Hydroxyurea before stroke, n	2	6	0.20
Aspirin before stroke, n	2	3	0.99

mRS stands for modified Rankin Score; SD, standard deviation; NIHSS, National Institute of Health Stroke Scale; ET, essential thrombocythemia; BP, blood pressure; LDL, low density lipoprotein.

4. Discussion

This study and previous reports illustrate that ET can cause stroke via two mechanisms: First, ET can result in stroke in association with conventional stroke related pathologies such as atherosclerosis, atrial fibrillation and hypertensive cerebral small arteriopathy. Previous case series reported from European countries showed that lacunar stroke or atherosclerotic stroke subtypes prevail among the patients with ET [2,4], and about half of the patients in this study were combined with conventional stroke etiologies. Second, ET can independently initiate thromboembolic events by platelet activation/aggregation, and in this case lesion patterns are more likely to be multiple infarctions extending single vascular territory. Previous study among Asian ET patients reported that ET associated stroke can present with multiple watershed infarction pattern without arterial stenosis [3]. However, it is probable that hidden embolic source such as paroxysmal atrial fibrillation or patent foramen ovale had not been detected after index stroke [6]. Another limitation of the study is that half of the patients had not been through bone marrow examination, although recent guideline emphasizes bone marrow biopsy for the definite diagnosis of ET [1].

Old age and female sex are known to be risk factors for neurological deterioration and death after stroke among the general population [7], and our study found a similar trend among stroke victims with ET. It is interesting to find that low hemoglobin status, rather than platelet count, is associated with poor prognosis after stroke combined with ET. Previous reports also showed neutral association between platelet counts or combined gene mutation and neurological outcome among ET stroke patients [2–4]. Anemia can aggravate stroke in general by several mechanisms, such as lowering oxygen carrying capacity, compromising cerebrovascular autoregulation, increasing inflammatory mediators, and creating turbulent cerebral blood flow which can trigger thrombus migration and expression of platelet adhesion molecules [8]. Whether the correction of this modifiable risk factor could improve neurological outcome and optimal hemoglobin target to maximize neurological recovery after stroke with ET might be both interesting and important questions to be answered by future study.

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Disclosure

None.

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