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ORIGINAL COMMUNICATION

Specific mechanisms of subarachnoid hemorrhage accompanied by ischemic stroke in essential thrombocythemia: two case reports and a literature review

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Abstract

Background *JAK2* V617F mutation increases the risk of thrombosis, and both ischemic and hemorrhagic strokes can occur in essential thrombocythemia (ET). The mechanisms underlying ischemic stroke in ET are diverse, and hemorrhagic stroke has rarely been reported in ET.

Methods Among 627 stroke patients, those identified as having ET were investigated retrospectively. A comprehensive systemic literature search of the PubMed database was also conducted.

Results Two cases were extracted with the diagnosis of ET who developed SAH and then ischemic stroke. In Case 1, a 47-year-old woman developed SAH in the left high convexity. Eleven hours later, acute cerebellar infarction suddenly developed due to right vertebral artery dissection. In Case 2, a 70-year-old woman developed SAH in the right high convexity. Magnetic resonance angiography showed multifocal stenotic changes in intracranial arteries. Three days later, she developed acute brain infarcts in the right middle cerebral artery territory. Eight weeks later, multifocal stenotic lesions improved. The literature review revealed 5 patients with hemorrhagic stroke and 40 patients with ischemic stroke associated with ET. Age at onset varied, female gender predominated, and the frequency of *JAK2* V617F mutation was high. Atherosclerotic vascular risk factors were more common in ischemic stroke, but not in hemorrhagic stroke.

Conclusions The current study describes rare cases of SAH accompanied by ischemic stroke secondary to ET along with a review of the current literature, implying specific mechanisms for cerebral artery disorders associated with *JAK2* V617F mutation.

Keywords Essential thrombocythemia · Subarachnoid hemorrhage · Ischemic stroke · *JAK2* V617F · Anagrelide

Background

Essential thrombocythemia (ET) is classified as a myeloproliferative neoplasm in the World Health Organization (WHO) classification [1]. Platelets are increased by deregulation of the hematopoietic stem cells, and the *JAK2* V617F mutation is observed with high frequency among ET patients [1, 2]. ET causes thrombotic and hemorrhagic complications, which contribute to mortality and morbidity [1, 3, 4]. After *JAK2* V617F was identified, risk stratification for thrombosis in ET was proposed, and the presence of *JAK2* V617F was shown to elevate the risk of thrombosis [1, 4, 5].

In recent years, considerable interest has been shown in cerebrovascular accidents such as ischemic and hemorrhagic strokes among patients with ET [6–12]. Although several case series studies and single case reports have demonstrated the clinical characteristics, stroke subtype, radiological and laboratory data, presence of *JAK2* V617F mutation, and therapy for cerebrovascular diseases in ET, the underlying mechanisms are yet to be fully elucidated.

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In the present study, we report two cases of ET with prior treatment using anagrelide in which subarachnoid hemorrhage (SAH) was accompanied by ischemic stroke. A comprehensive review of the literature was conducted to explore the clinical characteristics of ET patients developing cerebrovascular diseases.

Materials and methods

Case reports

From November 2015 to February 2018, 627 patients with cerebrovascular diseases including ischemic and hemorrhagic strokes were admitted to the Department of Neurology, Juntendo University Hospital. We retrospectively investigated stroke patients who had been identified as having ET from chart reviews. Data obtained from medical charts included patient characteristics (age, sex, atherosclerotic risk factors, and previous history of stroke), findings from computed tomography and magnetic resonance imaging (MRI) of the brain, stenosis of intracranial arteries on magnetic resonance angiography (MRA), 12-lead electrocardiography, carotid ultrasonography, and transthoracic echocardiography. This study was conducted in accordance with the Declaration of Helsinki. The independent ethics committee at Juntendo University Hospital approved this study (19-034). We obtained written informed consent from all patients before enrollment in the study.

Literature review

The literature review was carried out to identify case series and single case reports regarding cerebrovascular diseases related to ET with comprehensive data including clinical characteristics, radiological findings, laboratory data, *JAK2* V617F mutation, therapy for ET prior to stroke, neurological symptoms, outcomes, and therapy after stroke. Cases were identified through a search of the PubMed database utilizing the search strings "essential thrombocythemia", "*JAK2*", "*JAK2* V617F", "stroke", "ischemic stroke", "hemorrhagic stroke", "intracranial hemorrhage", "subarachnoid hemorrhage", "brain infarction", and "cerebral artery dissection". Diagnosis of ET was based on the assessment of clinical and biological data according to WHO diagnostic criteria [1]. Reference lists of identified papers were searched to find additional papers not captured by the initial search strategy. All identified articles were fully read with the relevant information extracted and summarized.

Results

During the study period, three stroke patients were identified as having ET (0.48%). Among these, we extracted two rare cases with the diagnosis of ET who initially developed SAH followed by ischemic stroke from our registry. The literature search (searching from 2008 to 2018 on PubMed) identified 45 cases.

Case presentation

Case 1

A 47-year-old Japanese woman with a previous history of abortion but lacking atherosclerotic vascular risk factors had been diagnosed with ET with *JAK2* V617F mutation. She had been treated using anagrelide at 0.5 mg/day for 2 months, then 1.5 mg/day for the subsequent 2 months. She had also been treated with aspirin at 100 mg/day for 9 months, but aspirin was stopped 3 months before stroke after platelet count was found to be elevated (1070×10^9/L). The patient experienced a sudden onset of headache in the left parietal region and was referred to our hospital. Blood pressure was 140/79 mmHg without arrhythmia. No neurological deficits other than pain in the left parietal region were identified. Laboratory testing showed marked elevations of both white blood cells (WBC, 33×10^9/L) and platelet count (1081×10^9/L), and decreased von Willebrand factor (vWF, 17%), leading to the diagnosis of acquired von Willebrand syndrome (AVWS). Brain CT showed SAH in the left high convexity (Fig. 1a). Contrast-enhanced three-dimensional CT showed no intracranial vascular malformations, arterial narrowing, or aneurysms. MR venography showed no occlusion of the superior sagittal sinus. SAH was treated with nifedipine and tranexamic acid. Eleven hours after the development of SAH, she suddenly presented with dysarthria, right-sided hemiparesis, cerebellar ataxia, and sensory deficits on the left side of the body. National Institutes of Health Stroke Scale (NIHSS) score was 4. MRI of the brain showed acute brain infarct in the right cerebellar hemisphere, cervical spinal cord, and medulla oblongata, and occlusion together with intramural hematoma in the right vertebral artery (Fig. 1b–f) [13, 14]. SAH owing to AVWS was thus diagnosed, followed by right cerebellar infarction associated with vertebral artery dissection. She was treated with aspirin at 100 mg/day and hydroxyurea at 1000 mg/day in place of anagrelide. Two weeks after therapy, WBC and platelets had decreased to 8.9×10^9/L and 280×10^9/L, respectively. Two months later, NIHSS score had improved to 2, and the patient was transferred to a rehabilitation hospital.

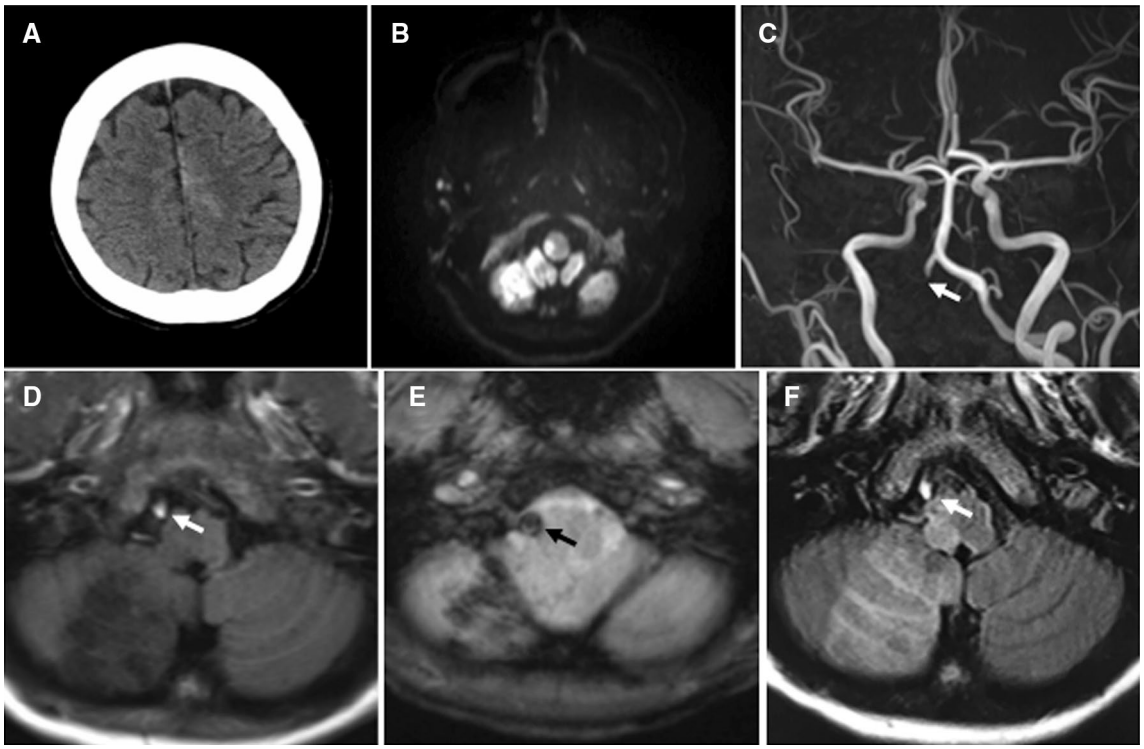

Fig. 1 Radiological studies in Case 1. **a** Unenhanced CT shows subarachnoid hemorrhage (SAH) at the left high convexity. **b** Diffusion-weighted imaging (DWI) shows acute brain infarction in the right cerebellum and cervical spinal cord. **c** MR angiography (MRA) shows occlusion in the right vertebral artery (arrow). **d–f** Representative images from T1-weighted (**d**), T2*-weighted (**e**), and fluid-attenuated inversion recovery (**f**) imaging show intramural hematoma in the right vertebral artery (arrows)

Case 2

A 70-year-old Japanese woman had a previous history of hypertension and *JAK2* V617F-positive ET, and had been treated with 100 mg/day of aspirin for 2½ years. She had also been treated with 1 mg/day of anagrelide for 3 months, then 3 mg/day of anagrelide for the next 3 months. She suddenly developed transient dysarthria and amnesia, and was referred to our hospital. Blood pressure was 168/90 mmHg without arrhythmia. Neurological examinations showed truncal ataxia, but NIHSS score was 0. Brain CT showed SAH in the right high convexity (Fig. 2a). MRA showed multifocal stenotic changes in bilateral anterior cerebral arteries (ACAs), middle cerebral arteries (MCAs), and posterior cerebral arteries (PCAs) (Fig. 2b). Laboratory data showed: WBC, 7.7×10^9/L; platelets, 666×10^9/L; and vWF, 182%. Cerebral angiography showed no intracranial vascular malformations or aneurysms. Anagrelide was stopped, and 100 mg/day of aspirin and 500 mg/day of hydroxyurea were started. Three days after admission, she developed transient left-sided hemiparesis. In brain MRI and MRA, acute brain infarcts were found in the territory of the right MCA (Fig. 2c), and multifocal stenotic lesions were still present in bilateral ACAs, MCAs, and PCAs. Cilostazol was added at 200 mg/day, and the patient did not show any further neurological deficits. Four weeks after admission, WBC was 3.0×10^9/L, platelet count was 260×10^9/L, and she was discharged. Follow-up MRI at 4 and 8 weeks after development of SAH showed that stenotic lesions in bilateral ACAs, MCAs, and PCAs had markedly improved (Fig. 2e, f). She did not present with any headache during the entire period. Case 2 displayed reversible multifocal stenoses on repetitive MRA, but symptoms differed from reversible cerebral vasoconstriction syndrome (RCVS), in which headache is common and the angiographic maximum point occurs 2–3 weeks after onset [15, 16]. The final diagnosis was RCVS mimic, as a cause of SAH in the territory of the right ACA accompanied by brain infarction in the territory of the right MCA.

Summary of the literature review

After 2008, when the WHO diagnostic criteria were updated to include the presence of *JAK2* V617F mutation, 5 single case reports with hemorrhagic stroke (Table 1) and 4 case series (37 cases) with ischemic stroke secondary to ET were identified (Table 2). Dissection of the cerebral artery was the underlying mechanism of stroke in Case 1, so the literature review identified five cases with ischemic stroke

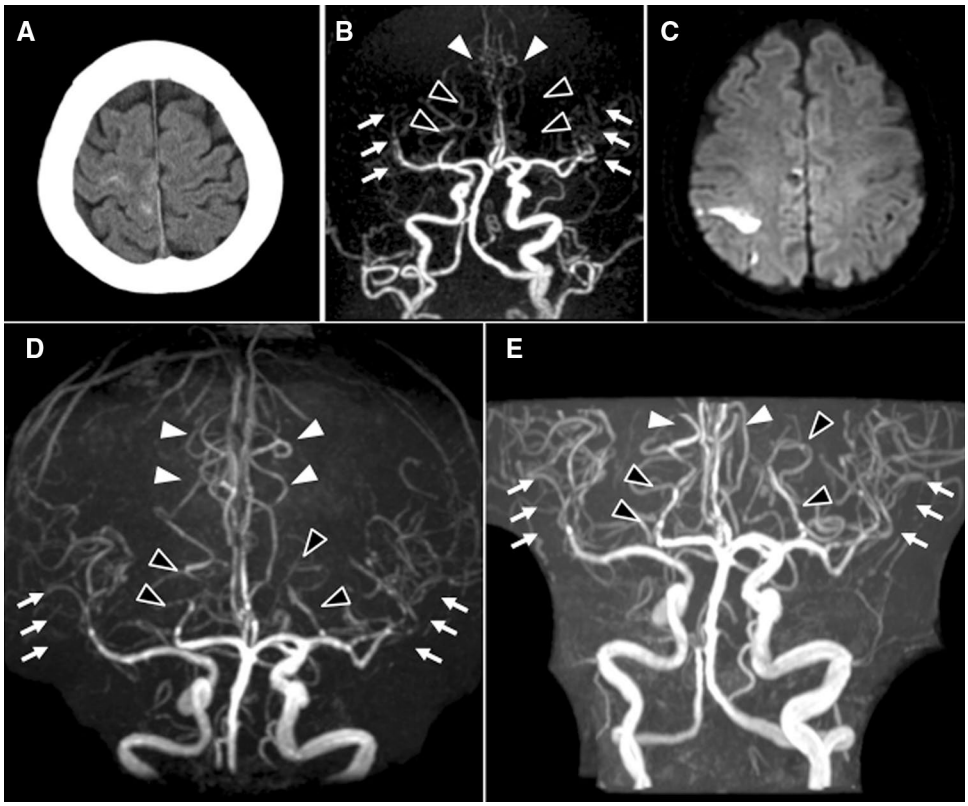

Fig. 2 Radiological studies in Case 2. **a** Unenhanced CT shows subarachnoid hemorrhage (SAH) at the right high convexity. **b** MR angiography (MRA) on admission shows stenosis in bilateral anterior cerebral arteries (ACAs, white arrowheads), middle cerebral arteries (MCAs, arrows), and posterior cerebral arteries (PCAs, arrowheads with white lines). **c** Diffusion-weighted imaging (DWI) shows acute brain infarction in the right cerebral hemisphere. **d**, **e** MRA 4 weeks (**d**) and 8 weeks (**e**) after stroke shows multifocal stenotic lesions in bilateral ACA (white arrowheads), MCAs, (arrows) and PCAs (arrowheads with white lines) have improved over time

with cerebral artery dissection, comprising three single case reports and two patients from two case series (Table 3). In total, 40 cases of ischemic stroke secondary to ET were identified. No reports with RCVS were found.

Among 45 patients identified through the current literature review, age at stroke onset ranged from 18 to 83 years for all strokes, and 30 patients were female (67%). Hypertension, diabetes mellitus, dyslipidemia, and current smoking were found in 27 patients (60%), 6 patients (13%), 18 patients (40%), and 11 patients (24%), respectively. In particular, frequencies of hypertension, dyslipidemia, and current smoking in hemorrhagic and ischemic strokes were 26 (65%) and 1 (20%), 18 (45%) and 0 (0%), and 11 (28%) and 0 (0%), respectively. *JAK2* V617F mutation was positive in 30 of the 38 patients (79%) who were genetically examined. Antithrombotic agents and treatment for ET were not performed in hemorrhagic stroke, while antithrombotic agents and hydroxyurea were often used in ischemic stroke patients.

Discussion

We encountered two rare cases of women with ET who developed SAH accompanied by ischemic stroke, and our literature review revealed eight single case reports and four case series for stroke associated with ET since the updated WHO diagnostic criteria included the presence of *JAK2* V617F mutation. To the best of our knowledge, the current study represents the first literature review of ET patients developing cerebrovascular diseases with comprehensive data, showing the clinical aspects of ischemic and hemorrhagic strokes secondary to ET. More importantly, the current study provides the first two case reports of ET patients developing SAH accompanied by ischemic stroke, with *JAK2* V617F mutation and pretreatment with anagrelide.

A large-scale study showed that systemic thrombotic events manifested more frequently than hemorrhage in ET, and age > 60 years, previous history of thrombosis, presence of atherosclerotic risk factors, leukocytosis, and presence of *JAK2* V617F mutation increased the risk of arterial thrombotic events [1, 4, 5]. With regard to ischemic stroke, several studies have focused on the association of ischemic stroke with ET, revealing ischemic stroke attributed to ET in < 0.6% of cases [7, 12, 17]. The mechanisms contributing to the development of ischemic stroke related to ET appear heterogeneous, from major ischemic stroke subtype such as atherothrombotic infarction and lacunar stroke, to particular pathogeneses such as thrombus in the carotid artery, hemodynamic infarction, and cerebral artery dissection [6, 7, 9, 10, 18]. Some case series have clarified frequent clinical characteristics of female sex, atherosclerotic vascular risk factors, and prior use of anti-thrombotic agents [6, 7, 19, 20]. The *JAK2* V617F mutation was positive in a majority of patients, and half of the patients in two studies were

Table 1 Previously reported cases and our two cases with hemorrhagic stroke secondary to essential thrombocythemia

References	Year	Age/sex	Atherosclerotic vascular risk factors	Treatment for ET before stroke	Location of hemorrhage	Type of hemorrhagic stroke	Platelet count, × 10^9/L	Leukocyte count, × 10^9/L	JAK2 V617F mutation	Neurological symptoms	Outcomes	Therapy after hemorrhagic stroke	Remark
Kondlapudi et al. [23]	2009	41/M	None	None	Left frontal lobe	ICH	935	29	NE	Aphagia	Recovery	HU	None
Miller et al. [11]	2010	21/M	None	None	Cerebellum	ICH	905	NA	Positive	Seizure	Ataxia and visual acuity disorder	HU	Unfractionated heparin administered beforehand for CVT
Adam et al. [8]	2014	32/F	None	None	Cerebellum	ICH	975	NA	Positive	Ataxia and consciousness disturbance	Recovery	VKA, HU	None
Baek et al. [22]	2014	42/M	None	None	Basal cistern	SAH	660	NA	NE	Consciousness disturbance	Recovery	None	Coil embolization for left SCA aneurysm was performed
Charles et al. [21]	2016	83/F	HT, DM	None	Right lateral ventricle	IVH	1097	8.8	NE	Headache	Recovery	None	None
Our Case 1	2019	47/F	None	Anagrelide	Left high convexity	SAH	1081	33	Positive	Headache	Recovery	Asp, HU	Brain infarction occurred 11 h later
Our Case 2	2019	70/F	HT	Anagrelide	Right high convexity	SAH	666	7.7	Positive	Dysarthria and amnesia, truncal ataxia	Recovery	Asp, Cilo, HU	Aspirin was pretreated, brain infarction occurred 3 days later

ET essential thrombocythemia, *JAK2* Janus activating kinase 2, *ICH* intracranial hemorrhage, *NE* not examined, *HU* hydroxyurea, *NA* not available, *CVT* cerebral venous thrombosis, *VKA* vitamin K antagonist, *SAH* subarachnoid hemorrhage, *SCA* superior cerebellar artery, *HT* hypertension, *DM* diabetes mellitus, *IVH* intraventricular hemorrhage, *Asp* aspirin, *Cilo* cilostazol

Table 2 Previously reported case series with ischemic stroke secondary to essential thrombocythemia

References	Year	Number of cases (events)	Age, years	Female gender	Atherosclerotic vascular risk factors	Prior antithrombotic therapy	Treatment for ET before stroke	Platelet count, × 10^9/L	Leukocyte count, × 10^9/L	JAK2 V617F mutation	Outcome	Antithrombotic therapy after stroke	Treatment for ET after stroke
Richard et al. [6]	2011	14	61 ± 16 (45–82)	9	HT, 5; DM, 1; DL, 6; smoking, 5; AF, 1	Asp, 2; Clop, 1; VKA, 2	None	714±269 (407–1431)	11.0±4.0[a] (7.1–20.4)	Positive, 8; NE, 1	Recovery, 8; sustained neurological deficits, 6, death, 0	Asp, 13; VKA, 4[b]	HU, 10; IFN, 1[b]
Pósfai et al. [19]	2014	11 (18)	67 ± 11 (45–82)	7	HT, 11; DM, 1; DL, 6; smoking, 2; PAD, 4	Asp, 7; Clop, 2	HU, 5	501 ± 134 (320–885)	NA	Positive, 11	NA	Asp, 2; Clop, 10;	HU, 6
Kato et al. [7]	2015	10 (13)	65 ± 21 (18–83)	7	HT, 8; DM, 1; DL, 4; smoking, 1; AF, 1; CAD, 1; PAD, 1	Clop, 7; Cilo, 4; Dipy, 1	HU, 4	966 ± 383 (416-1618)	11.5±6.5 (3.6-22.7)	Positive, 5; NE, 3	Recovery, 8; sustained neurological deficits, 5, death, 0	Asp, 2; Clop, 10; Cilo, 4; Dipy, 1, VKA, 1	HU, 12
Trifan et al. [20]	2018	2	81, 67	2	HT, 2; DM, 2; DL, 2; AAA, 1	None	None	573[c], 700[c]	NA	Positive, 2	NA	VKA, 2;	HU, 1

ET essential thrombocythemia, *JAK2* Janus activating kinase 2, *HT* hypertension, *DM* diabetes mellitus, *DL* dyslipidemia, *AF* atrial fibrillation, *Asp* aspirin, *Clop* clopidogrel, *VKA* vitamin K antagonist, *NE* not examined, *HU* hydroxyurea, *IFN* interferon, *PAD* peripheral artery disease, *NA* not available, *CAD* coronary artery disease, *Cilo* cilostazol, *Dipy* dipyridamole, *AAA* abdominal aortic aneurysm

[a]Not available in 2 cases, and average and standard deviation in 12 cases

[b]First-line therapy is shown

[c]Maximum values during admission

Table 3 Previously reported cases with ischemic stroke due to cerebral artery dissection secondary to essential thrombocythemia

References	Year	Age/sex	Atherosclerotic vascular risk factors	Treatment for ET before stroke	Involvement of dissection	Platelet count, $\times 10^9$/L	Leukocyte count, $\times 10^9$/L	JAK2 V617F mutation	Neurological symptoms	Therapy after hemorrhagic stroke	Remark
D'Ambrosio et al. [10]	2008	57/F	Smoking	None	Right ICA	426, 872[a]	NA	NE	Left arm weakness and facial palsy, and dysarthria	LMWH, HU[c]	Ischemic heart disease occurred after 3 months and PCI was performed
Richard et al. [6]	2011	47/M	Smoking	None	Left VA	750	11.6	Negative	Recovery	VKA, HU	None
Freilinger et al. [9]	2011	43/F	Smoking	None	Right ICA	550	Normal	Positive	Left brachiofacial weakness and hemineglect	VKA, HU	None
Verdure et al. [18]	2012	37/F	Smoking	None	Bilateral VA	955	14.7	Positive	Vertigo, oculomotor palsy, and cerebellar ataxia	OAC, HU	Chiropractic manipulation for torticollis was performed 4 days before stroke. cerebellar infarction recurred after 2 weeks
Kato et al. [7]	2015	52/F	HT, DL	None	Left MCA	554	10.2	Positive	Mild aphasia	Clop, HU	None

ET essential thrombocythemia, *JAK2* Janus activating kinase 2, *ICA* internal carotid artery, *NA* not available, *NE* not examined, *LMWH* low molecular weight heparin, *HU* hydroxyurea, *PCI* percutaneous coronary intervention, *VA* vertebral artery, *VKA* vitamin K antagonist, *OAC* oral anticoagulant, *HT* hypertension, *DL* dyslipidemia, *MCA* middle cerebral artery, *Clop* clopidogrel

[a]Platelet count at 6 months after stroke and diagnosis of ET

prior users of cytoreduction therapy. Thus, not only atherosclerotic vascular risk factors, but also ET itself appears to contribute to the development of ischemic stroke associated with ET under the treatment with anti-thrombotic therapy.

Conversely, hemorrhagic stroke has rarely been reported in ET [8, 11, 21–23]. The type of hemorrhagic stroke was diverse, including SAH, intracranial hemorrhage, and intraventricular hemorrhage, while our two cases developed SAH. In contrast to ischemic stroke, atherosclerotic vascular risk factors were infrequent, and no antithrombotic agents or cytoreduction therapies had been used previously. The *JAK2* V617F mutation was positive in all patients in whom genetic examination was performed. An excessive increase in platelets to $> 1000 \times 10^9$/L has been shown to induce AVWS, which can be associated with hemorrhage [24]. However, only one case displayed platelets $> 1000 \times 10^9$/L in the development of hemorrhagic stroke. The pathogenesis of hemorrhagic stroke in ET thus remains to be elucidated.

ET patients with cerebral artery dissection developing ischemic stroke show similarities in terms of the female preponderance and common *JAK2* V617F mutation, but differences in the infrequency of major atherosclerotic vascular risk factors and pretreatment with antithrombotic agents and cytoreduction therapy, compared to overall ischemic stroke patients with ET. These clinical characteristics were consistent with cerebral artery dissection in stroke patients without ET, especially when occurring in young adults [25].

In the present study, our two cases initially developed SAH, then infarction in the right cerebellar hemisphere after 11 h in Case 1, and in the right cerebral cortex after 3 days in Case 2. Case 1 showed extreme elevation of platelets $> 1000 \times 10^9$/L and decreased vWF, and brain MRI elucidated intramural hematoma in the right vertebral artery. We thus diagnosed AVWS as a cause of SAH, and cerebral artery dissection as the cause of cerebellar infarction. In Case 2, platelet count was 666×10^9/L, and vWF was 182% in the occurrence of SAH, which did not reach the diagnosis of AVWS. Repetitive MRAs revealed that the involvement of bilateral ACAs, MCAs, and PCAs was conspicuous at the onset of SAH, and improved from onset to 2 months later. Case 2 displayed reversible stenosis of multifocal intracranial arteries, but the angiographic maximum point was at the onset of SAH rather than 2–3 weeks after onset, characteristic headache was absent, and the final diagnosis was RCVS mimic, which might be a cause of SAH and right cortical infarction [15, 16]. On the other hand, several studies elucidated that endothelial injuries associated with *JAK2* V617F mutation were induced in ET [22, 26–28]. In particular, *JAK2* V617F mutation induces pronounced activation of platelet–leucocyte interactions as well as increased expression of P-selectin on the platelet surface, leading to a hypercoagulable state and the formation of leukocyte–platelet mixed aggregates [26]. It is suggested that ET with *JAK2* V617F mutation may cause a hypercoagulable state and disturbance of the microcirculation within the vasa vasorum in the cerebral arteries, increasing the vulnerability of the arterial wall, and thereby damaging the endothelium of the cerebral arteries. Collectively, cerebral artery dissection in Case 1 and RCVS mimic in Case 2 suggested a common pathogenesis of endothelial injury in cerebral arteries associated with *JAK2* V617F mutation. Further study is warranted.

Each of the patients in our cases had been treated with anagrelide prior to the development of cerebrovascular diseases. Anagrelide is an oral imidazo-quinazoline derivative, and selectively lowers platelets by affecting megakaryocyte maturation [29]. The ANAHYDRET study showed no inferiority of anagrelide compared with hydroxyurea in preventing thrombotic complications among patients with ET [30]. To date, thrombotic and hemorrhagic complications linked with long-term anagrelide treatment in ET patients have been reported [31]. On the other hand, two cases had been treated with aspirin before stroke onset, but aspirin was stopped in Case 1, because the platelet count increased to $> 1000 \times 10^9$/L together with AVWS. Aspirin was shown to reduce thrombotic events in *JAK2* V617F mutation-positive ET, but increased hemorrhagic events in patients with platelet counts $> 1000 \times 10^9$/L [32], consistent with our therapeutic strategy before stroke development. Taken together, the direct mechanisms behind the association of pretreatment by anagrelide and aspirin with SAH accompanied by ischemic stroke owing to endothelial injury in cerebral vessels in our cases remain essentially unknown.

The current study has some potential limitations. This was a retrospective study, and platelet counts before, during, and after stroke were not monitored for all patients. Furthermore, genetic examinations and bone marrow analyses were not conducted in patients with platelet counts continuously elevated to $> 450 \times 10^9$/L. Some ET patients among our stroke patients might thus have been overlooked.

In conclusion, our first literature review elucidated that the comprehensive clinical aspects of stroke secondary to ET, and that type of stroke and its pathological mechanisms were diverse. Among these, we report two rare cases of SAH accompanied by ischemic stroke occurring in ET, in which specific mechanisms of cerebral endothelial injury related to *JAK2* V617F mutation may be implicated. In the case of SAH accompanied by ischemic stroke, investigations for disorders of cerebral large arteries associated with *JAK2* V617F mutation are critical. Further study to explore these stroke mechanisms is warranted.

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Compliance with ethical standards

Conflicts of interest Authors declare that they have no conflicts of interest.

Ethical approval This study was conducted in accordance with the Declaration of Helsinki. The independent ethics committee at Juntendo University Hospital approved this study (19-034).

Informed consent We obtained written informed consent from all patients before enrollment in the study.

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