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Essential thrombocythemia with CALR mutation and recurrent stroke: two case reports and literature review

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***Abstract*:** Cerebrovascular events, especially ischemic stroke, are common complications of essential thrombocythemia (ET). Compared to JAK2V617 F mutation, CALR mutation is considered as a lower risk factor of thrombosis in ET. Until now stroke in ET with CALR mutation has rarely been reported. We retrospectively investigated patients diagnosed with stroke and ET in Xijing hospital of Air Force Medical University, from 2015 to 2021. Clinical characteristics (including medical history, physical and auxiliary examination and prognosis) were recorded and associated literature was reviewed. Among the 19 patients diagnosed with both stroke and ET we retrieved, two cases were positive for CALR mutation. In case 1, a 71-year-old man developed the first ischemic event under the treatment of anagrelide, followed by a hemorrhagic stroke after receiving aspirin and clopidogrel for 4 months. Ischemic stroke reccurred and the neurological function deteriorated progressively. In case 2, a 44-year-old man presented with hypoxic-ischemic encephalopathy due to serious myocardial infarction and subsequent brain imaging indicated three times of ischemic stroke events. The patient gradually got improved through cytoreductive and antiplatelet therapy and rehabilitation. Literature review showed that cerebrovascular event is the most serious neurological complication of ET and may be the presenting symptom. Most of reported cases with ET accompanied by stroke were positive for JAK2 V617 F mutation, but with rare CALR mutation. ET with CALR mutation can cause both hemorrhagic and ischemic stroke. Identification of such rare causes of stroke is of great importance to provide precise and individualized prevention and therapy.

Keywords: CALR mutation, essential thrombocythemia, stroke

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Background

Essential thrombocythemia (ET) is a chronic myeloproliferative neoplasm (MPN) characterized by platelet count $>450\times10^9$/L and megakaryocytes proliferation in the bone-marrow (BM), with an incidence of 1.2 to 3.0 per 100,000 population per year.[1] Many neurological symptoms may manifest in patients with ET, including nonspecific symptoms and stroke events. Nonspecific features include headaches, visual disturbances, lightheadedness and dysesthesia, whereas stroke is a complication of ET with severe morbidity and mortality.[2] Diagnosis of ET accords to the 2016 WHO criteria.[3] Most patients with ET harbor a mutation in one of three genes: JAK2 (V617 F) (in 55%), CALR (in 15%-24%), or MPL (in 4%).[4] Since the presence of JAK2 (V617F) was shown to elevate the risk of thrombosis, cases of stroke related to ET reported mainly involved in JAK2 (V617F) mutation. Until now cases of stroke related to ET with CALR mutation have been rarely reported.

The purpose of this article is to report two cases of ET with CALR mutation accompanied by stroke. A comprehensive review of the literature

was also conducted to explore the clinical characteristics and pathogenesis of ET patients developing cerebrovascular diseases.

Materials and methods

Case reports

We searched the electronic medical record system of Xijing hospital of Air Force Medical University and extrated 19 patients diagnosed with stroke and ET in department of neurology, among which two cases positive for CALR mutation. The clinical information including symptoms, laboratory tests, auxiliary examinations, gene mutation, radiological findings and prognosis was collected and reported.

Literature review

To identify case series and case reports with regard to cerebrovascular disease and ET the literature review was carried out. Search terms of 'Essential Thrombocythemia', 'stroke', 'cerebral infarction', 'cerebral thrombosis', 'cerebral hemorrhage', 'cranial hemorrhage' and 'CALR' were used to search the Pubmed database. The comprehensive data including clinical characteristics, risk factors of cerebrovascular diseases, platelet counts, gene mutation types, neurological symptoms, times of stroke events, radiological findings, therapy for ET after stroke and outcome was summarized.

Case presentation

Case 1

A 71-year-old man with previous history of ET with CALR mutation ceased to take hydroxyurea and interferon because of intolerance of adverse effect and began to use anagrelide at 1 mg~1.5 mg/day adjusted according to platelet counts (300-600$\times10^9$/L) for 10 months before admission to our hospital. There was no history of stroke risk factors (e.g. hypertension, diabetes mellitus, coronary heart diseases, atrial fibrillation, smoke or alcohol abuse, carotid artery disease). The medical record in 2016 was reviewed and the BM biopsy indicated proliferation mainly of the megakaryocyte with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. Panel for myeloproliferative neoplasms related genes were performed and CALR1 mutation was identified. He felt paroxysmal dizziness and lower limbs weakness once or twice a day in November, 2019. Brain magnetic resonance imaging (MRI) showed acute infarction lesion nearby posterior horn of left lateral ventricle (Figure 1(a)). He was treated in local hospital and relieved after withdrawal of anagrelide and administration of aspirin and clopidogrel in the first 3 weeks, then aspirin at 100 mg/day, combination with atorvastatin at 20 mg/day. On March 9, 2020, he suddenly developed limb weakness without loss of consciousness and head computed tomography (CT) scan showed a hematoma in the right frontal lobe (Figure 1(b)). After then, aspirin and clopidogrel were stopped and anagrelide was represcribed. On March 14, 2020, he developed right hemiplegia, speech disorder, urine and feces incontinence and psychiatric disorder. Head diffusion weighted imaging(DWI) revealed multiple scattered acute infarcts involved in left basilar ganglion region, left posterior horn of lateral ventrical, cingulate gyrus, left cerebral lobes and right centrum semiovale (Figure 1(b)–(e)). Unfortunately he developed left hemiplegia and lethargy on April 12 of 2020 and head MRI showed a large acute infarct in the right parietal lobe(Figure 1(f)). He was referred to our hospital in April of 2020 due to recurrent stroke events. On admission, neurological examinations showed mental disorder, severe intelligent impairment and speech disorder. National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin Scale (mRS) scores were 14 and 5 respectively. Laboratory data showed: white blood cell (WBC), 10.44$\times10^9$/L(3.5-9.5); platelet, 566$\times10^9$/L(125-350); thromboelastogram (TEG), angle,79.2(53-72deg), maximum amplitude(MA), 80.3(50-70mm); serum total cholesterol, 5.17 mmol/L(3.1-5.69); Low density lipoprotein cholesterol (LDL-C), 2.4 mmol/L(0-3.36). Laboratory tests relevant to arteritis and tumor markers were not remarkable. Magnetic resonance angiography (MRA) found intracranial cerebral atherosclerosis and stenosis in left anterior cerebral artery (ACA) (Figure 1(h)). Magnetic resonance venography (MRV) showed no occlusion of any cerebral venous sinus. Atrial premature beats of 1957 times were found by 24 h-holter monitor. Cardiac ultrasound, aortic ultrasound and cervical artery ultrasound were not remarkable. Anagrelide 1 mg twice a day and interferonα2a 300wu every other day were commenced on the advice of the hematologists meeting. Platelet counts were controlled to 137-336$\times10^9$/L and no stroke event recurred during hospitalization. NIHSS and mRS were not improved either. However the patient experienced stroke

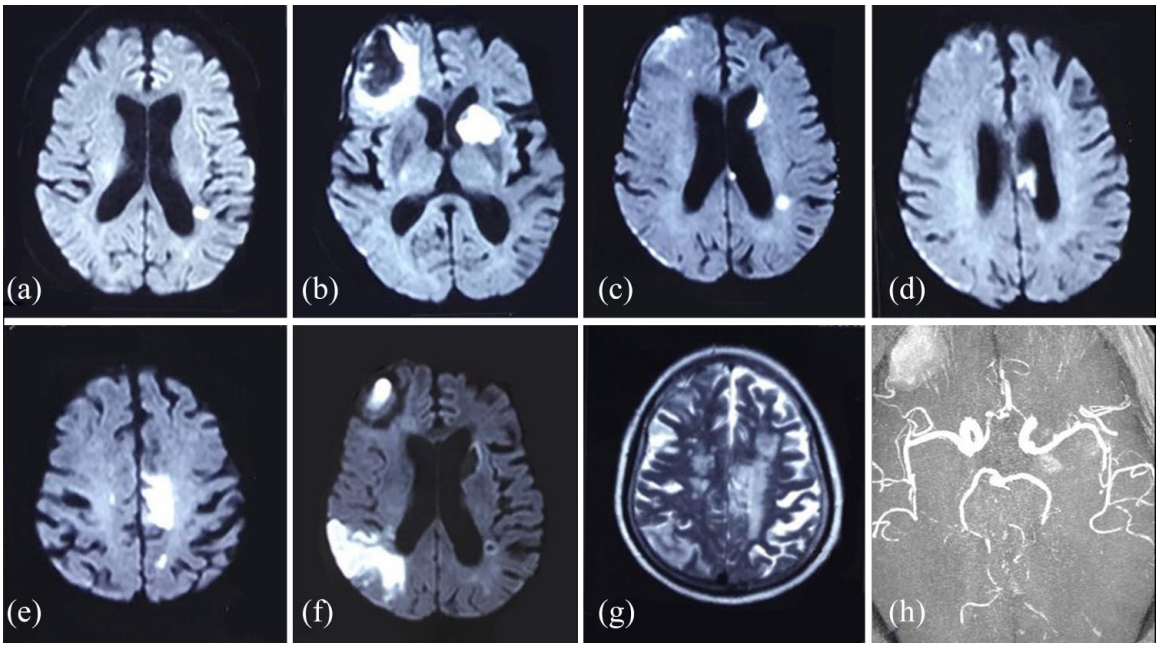

Figure 1. Radiological findings in case 1. Diffusion weighted imaging (DWI) showed acute cerebral infarction nearby posterior horn of left lateral ventricle as a result of the first episode of stroke (a). A hematoma located in the right frontal lobe induced by the second episode of stroke (b). Multiple scattered acute cerebral infarction lesions include left basilar ganglion region, left posterior horn of lateral ventricles,cingulate gyrus, left cerebral lobes and right centrum semiovale in the third episode of stroke (b, c, d, e). Large acute cerebral infarction lesion showed in the right occipitotemporal lobe in the fourth episode of stroke (f). T2-weighted imaging of brain magnetic resonance imaging(MRI) revealed massive white matter lesions in centrum semiovale (g). Magnetic resonance angiography(MRA) indicated intracranial cerebral atherosclerosis(h).

events twice in 4 months after discharge and his neurological symptoms deteriorated.

Case 2

A 44-year-old man had a previous history of ET diagnosed in 2013 and had been treated with interferon and hydroxyurea which were stopped 2 years ago due to intolerance of the plural effects. He experienced ischemic stroke in right parietal lobe and was found to have carotid artery atherosclerosis and dyslipidemia in 2020, since when aspirin 100 mg/day and atorvastatin 20mg/d were prescribed to prevent ischemic stroke. In February 2021, he developed ventricular fibrillation due to acute myocardial infarction and survived, but lost consciousness, after cardiopulmonary resuscitation (CPR) in local hospital. He was admitted to our hospital for further treatment in April, 2021. We reviewed the medical record of local hospital and found that platelet counts $> 759\times10^9$ /L during hospitalization; hypersensitive cardiac troponin *T*(cTnT), 641 ng/ml; electrocardiogram (EEG) indicated myocardial infarction and brain CT scanned after CPR showed cerebral infarction in temporo-parietal lobe (Figure 2(a)). He was treated with clopidogrel 75 mg/day, low molecular weight heparin (LMWH) 5000iu twice per day and interferon a-2a 250 million international units (IU) /day, but brain CT performed again during hospitalization in local hospital revealed cerebral infarction worsened. Unfortunately, during hospitalization in our department cerebral infarction worsened again and brain diffusion weighted imaging (DWI) showed acute infarcts located in right frontal and parietal lobes, bilateral occipital lobes and bilateral periventricular (Figure 2(b)–(d)). The MRA and MRV were not remarkable (Figure 2(e)). The platelet count was 516×10^9 /L at the meantime. Laboratory tests relevant to arteritis and tumor markers were not remarkable. BM biopsy was carried out and identified obvious proliferation of the megakaryocytes with enlarged, hyperlobulated and clustered ones on HE staining and Wright's staining (Figure 2(f)–(h)). Whole exome sequencing (WES) indicated CALR1 mutation. He was treated using interferon a-2a 250 million IU /day combined

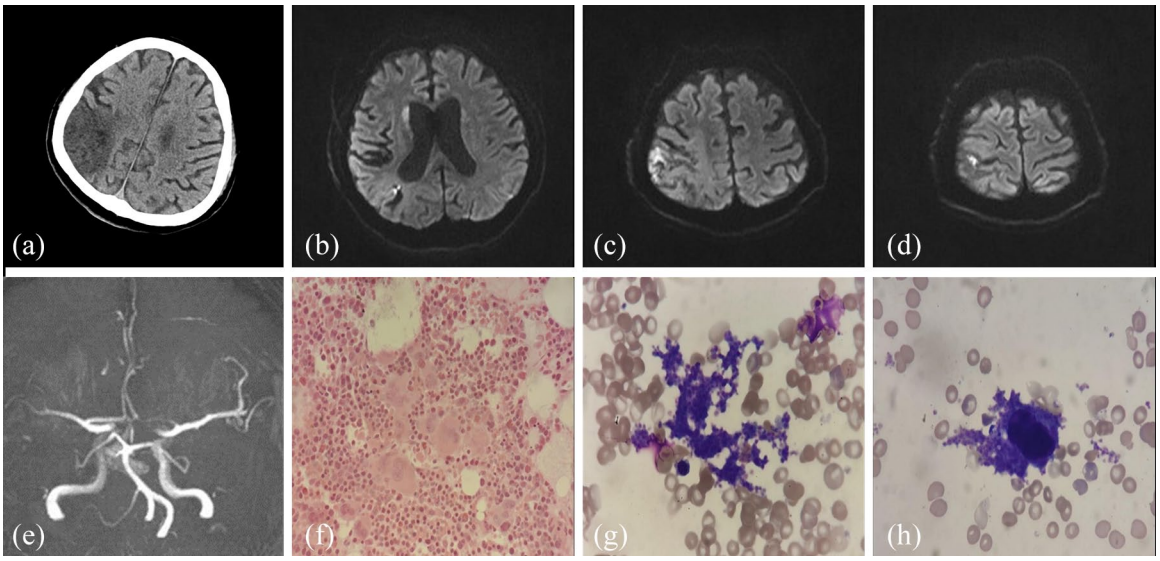

Figure 2. Radiological and bone marrow biopsy findings in case 2. Brain computed tomography (CT) after episode of myocardial infarction showed a massive infarction lesion located in right temporoparieto-occipital lobe (a). Subsequent diffusion weighted imaging (DWI) revealed acute multiple acute infarcts scattered in frontoparietal lobe, bilateral occipital lobes and right paraventricular (b, c, d). Magnetic resonance angiography (MRA) indicated intracranial arteries are not remarkable. Bone marrow biopsy showed obvious proliferation of the megakaryocytes with enlarged, hyperlobulated and clustered ones on HE staining and Wright's staining (f, g, h).

with aspirin and clopidogrel, along with rehabilitation. The patient recovered from disorder of consciousness state without stroke recurrence and discharged on April 26, 2021 with mRS of 5 scores. On follow-up of 2 months, hydroxyurea replaced interferon without antiplatelet agents for better cytoreductive effect and no stroke event recurred.

Summary of the literature review

Through searching pubmed database from 2004 to 2021, 24 single case reports (Table 1) and 5 case series including 39 cases (Table 2) with stroke secondary to ET were identified. Of the total 63 cases, 38 cases were JAK2 positive, 9 cases JAK2 negative, 1 case CALR1 positive and 15 of which without genes record. 55 cases were ischemic stroke (including cerebral infarction and TIA) secondary to ET and 8 cases were hemorrhagic stroke secondary to ET. Stroke was the initial symptom of ET in 39 cases (61.9%).46 cases (73%) had common cerebrovascular risk factors. In all, 29 cases (46%) experienced stroke events more than once. A total of 46 (73%) cases were treated with hydroxyurea as first line cytoreductive drug after stroke event, 27 (43.5%) cases of which were combined with mono-antiplatelet therapy(MAPT) . Aspirin (14 cases) and clopidogrel (10 cases) were most commonly used. Among the 38 (60%) cases with good prognosis, 32 (84.2%) cases were treated using hydroxyurea and 19 cases (51.4%) were combined with MAPT. (Table 3)

Discussion

ET is a rare risk factor of systemic thrombosis and cases referred to ET and cerebrovascular disease have been reported previously, of which most cases are ischemic stroke and positive for JAK2 mutation.[29,30] To our best knowledge, CALR mutated ET accompanied by recurrent cerebrovascular events were rarely reported.

Patients older than 60 years or with a previous history of thrombotic complication, JAK2 mutation, leukocytosis, smoking, hypertension, diabetes mellitus (DM) are at high risk of thrombosis.[4] Thrombosis attributed to ET can be shown as mild mirocirculation disorders including tinnitus, dizziness, migraine *et al.*, furthermore serious complications such as arterial thrombosis (myocardial infarction, cerebral infarct, TIA) and

Table1. Previously reported single cases of stroke secondary to essential thrombocythemia.

No.	References	Age	Sex (F/M)	Atherosclerotic vascular risk factors	Stroke as initial symptom of ET (yes/no)	Type of stroke	Times of stroke events	Platelet count, 10^9/L	Gene mutation	Therapy after stroke	Outcome
1	Mosso *et al.*[5]	40	F	recurrent abortion	Yes	CI, TIA	5	550	NA	Clop	No recurrence
2	Vemmos *et al.*[6]	65	F	DL	Yes	CI, TIA	6	1000	NE	HU Clop	Recovery
3	Ogata *et al.*[7]	62	M	None	Yes	CI, TIA	5	1020	NE	Ticlopidine HU	Died
4	Kornblihtt *et al.*[8]	18	F	None	Yes	CI, TIA	3	1480	NE	Anagrelide Asp Clop	recurrence
5	D'Ambrosio *et al.*[9]	57	F	smoking,	Yes	CI	1	426	NE	HU LMWH	Recovery
6	Kondlapudi *et al.*[10]	41	M	None	Yes	CH, SAH	1	935	NE	HU	Recovery
7	Kumar *et al.*[11]	45	M	smoking	Yes	CI	1	1000	JAK2 +	HU VKA	Recovery
8	Miller *et al.*[12]	21	M	None	Yes	CVST CH	1	905	JAK2 +	HU VKA	Recovery
9	Lazzaro *et al.*[13]	29	F	HT, DM	No	CI	3	1,080	JAK2-	Asp Clop CTX	Died
10	Freilinger *et al.*[14]	43	F	smoking	Yes	CI	2	550	JAK2 +	HU Asp	No recurrence
11	Verdure *et al.*[15]	37	F	smoking	Yes	CI	2	955	JAK2 +	HU OAC	Recovery
12	Kim *et al.*[16]	46	M	None	No	CI	1	720	NA	HU antiplatelet agents	Improved
13	Naganuma *et al.*[17]	69	M	HT	Yes	CI	4	874	NE	HU *Cilo*	No recurrence
14	Baek *et al.*[18]	42	M	HS	No	SAH	2	660	NE	None	Recovery
15	Adam *et al.*[19]	32	F	None	No	CH SAH	1	975	JAK2 +	HU Asp	Recovery
16	Fischer *et al.*[20]	74	M	None	No	CI	1	NA	JAK2 +	HU Asp	No recurrence
17	Pavaloiu *et al.*[21]	72	M	HT	Yes	CI	3	961	NA	HU antiplatelet agents	Improved
18	Huh *et al.*[22]	59	F	HT	Unkown	TIA CI	2	708	JAK2 +	VKA Clop	No recurrence

(Continued)

Table1. (Continued)

No.	References	Age	Sex (F/M)	Atherosclerotic vascular risk factors	Stroke as initial symptom of ET (yes/no)	Type of stroke	Times of stroke events	Platelet count, 10^9/L	Gene mutation	Therapy after stroke	Outcome
19	Yuan *et al.*[23]	63	F	None	No	CI	1	448	JAK2 +	LMWH	No recurrence
20	Wang *et al.*[24]	70	F	None	Yes	CI	1	466	JAK2 +	HU Asp Clop Heparin	Unkown
21	Roh *et al.*[25]	35	F	None	Yes	CVST	1	600	JAK2 +	Asp Apixaban	Recovery
22	Batista *et al.*[26]	81	F	AF, HT	Yes	TIA CI	3	810	JAK2 +	HU Apixaban	Recovery
23	Raza *et al.*[27]	34	F	HT	Yes	CI	1	539	NE	HU Asp Clop	No recurrence
24	Momozaki *et al.*[28]	33	F	none	no	CH	1	473	CALR1 +	None	Recovery

AF, atrial fibrillation; Asp, aspirin; CH, cerebral hemorrhage; CI, cerebral infarction; Cilo, cilostazol; Clop, clopidogrel; CTX, cyclophosphamide; CVST, cerebral venous sinus thrombosis; DL, dyslipidemia; DM, diabetes mellitus; ET, essential thrombocythemia; F, female; HS, Hereditary spherocytosis; HT, hypertension; HU, hydroxyurea; JAK2, Janus activating kinase 2; LMWH, low molecular weight heparin; M, Male; NA, not available; NE, not examined; OAC, oral anticoagulant; PSVT, paroxysmal supraventricular tachycardia; TIA, Transient Ischemic Attacks; SAH, subarachnoid hemorrhage; VKA, vitamin K antagonist.

venous thrombosis (cerebral sinus/venous thrombosis, deep venous thrombosis, pulmonary thrombosis) often occur.[30] Stroke is a serious neurological complication of ET with the prevalence of 3.7%. Even stroke can be the first manifestation of ET in almost 60% cases we reviewed.[29,31,34] Stroke and myocardial infarction can simultaneously occur in ET.[16,20] Stroke complicated with ET is more likely to recur and suffer from recurrent cerebrovascular events as many cases reported.[5–7] Therefore, ET may be one of the causes of recurrent stroke of unknown reasons. Nonetheless, it is easy to be misdiagnosed when platelet count within normal rang.[5,7,32] It is important to pay attention to platelet count of patient with stroke, since recurrence risk of stroke with ET can be decreased by cytoreductive and antiplatelet therapy.[31]

Recent researches illustrated that there were two ways for ET causing stroke. On one hand, ET can independently initiate cerebrovascular events by platelets activation/aggregation without common risk factors of cerebrovascular diseases. Under these circumstances, multiple scattered lesions involving multiple vascular territories were more prevalent, which is similar with the brain MRI/CT performance of the patient in case 1. On the other hand, ET can induce stroke in combination with other risk factors of cerebrovascular disease, such as atherosclerosis, atrial fibrillation and hypertensive cerebral small arteriopathy. In the case, the radiological characteristic may be lacunar stroke or atherosclerotic stroke subtypes, as well as white matter lesions and brain atrophy.[29,30,35]

Most cases of stroke with ET reported relate to JAK2 mutation in accordance with the thrombosis risk stratification in ET.[4,29,30] It has been showed that JAK2 mutation can lead to both structural and functional abnormality of red blood cells, white blood cells, platelets, as well as endothelial cells, which leads to increased cell aggregation, binding and activation of the endothelium causing increased risk of thrombosis.[36] CALR mutation is considered as a low-risk factor of thrombosis in patients with ET.[37] The mutant CALR leads to upregulation of megakaryocytic proliferation. Among ET patients with CALR mutations, there are two predominant variants: type 1 characterized by a 52 bp deletion and type 2 characterized by a 5 bp insertion. Compared to CALR2 mutation, patients with CALR1 mutation are more susceptible to

Table 2. Previously reported case series of stroke secondary to essential thrombocythemia.

References	Nomber of cases	Age ((years)	sex (No.)	Atherosclerotic vascular risk factors	Stroke as presenting symptom (n)	Type of stroke	Time of stroke events	Platelet count (10^9/L)	Gene mutation	Therapy after stroke	Outcome
Richard *et al.*[29]	14	34-87 (61)	M,5 F,9	DL (6/14) HT (5/14) Smoking (4/14) DM (1/14) ASA (1/14) CHD (1/14) AF (1/14) APA (1/14),	12 (14)	CI (10/14), TIA (3/14), CI + CH (1/14)	1 (14/14)	407-1431 (713)	JAK2 + (8/14)	HU + Asp (7/14), HU + Asp + VKA (3/14), IFN + Asp (1/14), HU + anagrelide + Asp (1/14) Asp + Clop (1/14), HU + IFN + anagrelide + Asp + VKA (1/14)	recover (5/14)
Pósfai *et al.*[30]	11	45-82 (66)	M,4 F,7	HT (8/11) DL (7/11) PAD (4/11) Smoking (2/11) DM (1/11) Obesity (1/11)	2 (11)	CI (6/14), CI + TIA (3/14), CH + TIA (1/14), TIA (1/14)	4 (1/14), 3 (2/14), 2 (4/14), 1 (4/14)	415-885 (536)	JAK2 + (11/11)	HU + clop (5/11), Clop (5/14), HU + Asp (1/14)	NA
Kato *et al.*[31]	10	18-83 (65)	M,3 F,7	HT (8/10) DL (3/10) DM (1/10) Smoking (1/10) AF (1/10)	8 (10)	CI (7/10), CI + TIA (3/10)	3 (2/10) 2 (4/10) 1 (4/10)	494-1618 (965)	JAK2 + (5/10)	HU + Clop (4/10), HU + Clop + Cilo (3/10), HU + Asp (1/10), HU + Dipy (1/10), HU + Asp + Sarp (1/10)	Recover 6 (10)
Trifan *et al.*[32]	2	1. 81; 2. 87	1.F 2.M	HT (2/2) DL (2/2) DM (2/2)	2 (2)	1. CI 2. CH	2 (2/2)	1. 573 2. 700	JAK2 + (2/2)	1. HU + VKA 2. VKA	NA
Sugiyama *et al.*[33]	2	1. 47; 2. 70	*F* (2/2)	1. None 2. HT	0 (2)	SAH + CI (2/2)	2 (2/2)	1. 1081 2. 666	JAK2 + (2/2)	1. HU + Asp 2. HU + Asp + Cilo	Recover

AF, atrial fibrillation; APA, Antiphospholipid antibody; ASA, atrial septal aneurysm; Asp, aspirin; CH, cerebral hemorrhage; CHD, coronary heart disease; CI, cerebral infarction; Cilo, cilostazol; Clop, clopidogrel; Dipy, dipyridamole; DL, dyslipidemia; DM, diabetes; F, female; HT, hypertension; HU, hydroxyurea; IFN, interferon; JAK2, Janus activating kinase 2; M, Male; No, number; PAD, peripheral arterial disease; SAH, subarachnoid hemorrhage; Sarp, sarpogrelate; TIA, Transient Ischemic Attacks; VKA, vitamin K antagonist.

Table 3. Characteristics of 63 reported cases of ET and stroke.

Characteristics	Description	n.(%)
Gender	Female	41(65.1)
Gene mutation type	JAK2 mutaion	38(60.3)
	CALR mutation	1(1.5)
	NA	15(23.8)
Stroke type	ischemic stroke	53(84.1)
	hemorrhagic stroke	6(9.5)
	mix type	4(6.3)
Presenting symptom	stroke	39(61.9)
Cerebrovascular risk factors	None	17(26.9)
	⩾ 1	46(73)
Times of stroke events	⩾ 2	29(46)
Post-stroke therapy	HU as cytoreductive drug	46(73)
	HU + MAPT	27(42.8)
	HU + DAPT	8(12.7)
	HU + others drugs	11(17.5)
Good prognosis		38(60.3)
	HU as cytoreductive drug	32(84.2)
	HU + MAPT	19(59.4)
	HU + other drugs	13(40.6)

CALR, Calreticulin; DAPT, dual antiplatelet therapy; HU, hydroxyurea; JAK2, Janus activating kinase; MAPT, mono-antiplatelet therapy; n, number; NA, not available.

thrombosis.[38] The patients in case 1 and case 2 were both positive for CALR1 mutation tested by polymerase chain reaction (PCR) panel for detecting myeloproliferative neoplasm associated genes and WES respectively. Even though most cases and case series reported did not provide genetic testing methods which might be affected by more attention to JAK2 mutation at higher risk of thrombosis, we speculate that strategy for genetic testing centering on JAK2 might miss CALR mutation.

The majority of cases with regard to ET related stroke had a good prognosis (improvement, recovery or no recurrence as reported in reviewed literature) through treatment using cytoreductive and antiplatelet medication,[14,19,31] specifically hydroxyurea combined with MAPT (aspirin or clopidogrel) used in most cases. However, the aforementioned strategy might not be beneficial to CALR mutation ones. A retrospective research conducted by Alvarez-Larrán *et al.*[39] showed that low-dose of aspirin does not reduce thrombosis frequency and may increase the major bleeding incidence of CALR mutated patients. Here, the patient in case 1 experienced hemorrhagic stroke in the condition of receiving aspirin combined with clopidogrel for antiplatelet therapy. Cytoreductive therapy may be preferable because of its efficiency of thrombosis prevention and low risk of associated bleeding in CALR mutated patients with marked thrombosis, however anagrelide is an exception. Previous research showed thrombotic and hemorrhagic complications related to long-term use of anagrelide in ET patients.[40] In addition, Sugiyama *et al.*[33] recently reported two cases of ET with prior treatment using anagrelide in which subarachnoid hemorrhage (SAH) was accompanied by ischemic stroke. Moreover, a recent CALR mutated case of ET was reported to develop cerebellar hemorrhage with long term use of aspirin and anagrelide. The patient in case 1 got treated ET with anagrelide because of intolerance of hydroxyurea. Thus antiplatelet therapy and anagrelide were implicated as bleeding risk of case 1. As the European LeukemiaNet recommended, peg-IFNα is the preferred option over hydroxycarbamide or anagrelide for CALR mutated ET.[41]

As to the relationship between platelet count and stroke risk, almost all cases of ET and stroke reviewed showed a quite high level of platelet count, no less than 400×10^9 /L, which is consistent with our two cases. The patient in case 1 suffered from recurrent stroke events while the platelet counts over 500×10^9/L and did not recur under strictly control of platelet counts between 137 and 336×10^9/L during hospitalization. For the patient in case 2 no stroke event recurred when the platelet count level decreased lower than 700×10^9/L. Normalization of platelet count seem to be beneficial to our two patients during hospitalization, which is recommended by the European LeukemiaNet.[41] It was a pity that von Willebrand factor (vWF) was not tested in case 1, since acquired von Willebrand syndrome (AVWS)was considered as a risk factor of bleeding in ET.[42] AWS testing plays an important

role in bleeding management strategies in MPNs proposed recently.[43]

In conclusion, the specific pathogenesis of CALR mutated ET concomitant with ischemic or hemorrhagic stroke remains to be elucidated. There are no standard or recommended treatment for ET accompanied by cerebrovascular disease and relevant large sample of randomized control study is urgently needed. It is important to pay attention to platelet count of patients with stroke and to identify type of gene mutation of patents with stroke and ET. Individualized therapy strategy specific to different gene mutation may benefit the patients with ET complicated with stroke.

Ethics statement approval and patient consent

This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patients or their legal guardians for the publication of medical data and related images. The study was approved by the Ethics Committees of Xijing Hospital, Air Force Military Medical University (KY20182024-1 F-).

Author contribution(s)

Rong Chen: Data curation; Formal analysis; Investigation; Methodology; Validation; Writing – original draft.

Xiaodan Shi: Data curation; Methodology; Writing – original draft.

Luojun Wang: Data curation; Methodology; Writing – review & editing.

Xuan Wang: Investigation; Writing – review & editing.

Jingya Wei: Investigation; Methodology; Writing – review & editing.

Xiaogang Kang: Supervision; Validation; Writing – review & editing.

Fang Du: Supervision; Validation; Writing – review & editing.

Shan Gao: Methodology; Visualization; Writing – review & editing.

Fang Yang: Conceptualization; Conceptualization; Project administration; Project administration; Supervision; Validation; Writing – review & editing.

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Conflict of interest statement

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