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Review

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Pathophysiology and Optimal Treatment of Intracranial Branch Atheromatous Disease

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Intracranial branch atheromatous disease (BAD) is a pathological condition characterized by the occlusion of a relatively large perforating branch (700–800 μm) near the orifice of a parent artery due to atherosclerotic plaque-based thrombus (microatheroma). BAD is refractory to treatment and follows a course of progressive exacerbation, especially motor paralysis. Uniform treatment for common atherothrombotic cerebral infarction or lacunar infarction does not prevent the progressive exacerbation of BAD, and consequently affects functional prognosis. To date, various combinations of treatments have been investigated and proposed to attenuate the worsening symptoms of BAD. However, no therapy with established efficacy is yet available for BAD. Since it is the most difficult condition to treat in the area of cerebral infarction, the establishment of optimal treatment methods for BAD is keenly awaited. This review presents an overview of the acute treatments available for BAD and discusses the prospects for optimal treatment.

Key words: **Branch atheromatous disease, Lenticulostriate artery, Alteplase, Dual-antiplatelet treatment**

Abbreviations: **BAD, branch atheromatous disease; CL, clopidogrel loading; DAPT, dual-antiplatelet treatment; END, early neurological deterioration; LSA, lenticulostriate artery; MCA, middle cerebral artery; rt-PA, recombinant tissue plasminogen activator; sICH, symptomatic intracranial hemorrhage; SSS, Stop Stroke Study; TOAST, Trial of Org IO172 in Acute Stroke Treatment**

Introduction

Intracranial branch atheromatous disease (BAD), an occlusion at the origin of a deep penetrating artery of the brain, was proposed as a pathological concept by Caplan *et al.*[1] based on the autopsy cases reported by Fisher *et al.*[2] in 1971. Unlike true lacunar infarcts that are characterized by hypertensive lipohyalinotic degeneration in the distal part of a perforating artery with a relatively small diameter (≤ 200 μm), BAD is characterized by the narrowing or occlusion of a relatively large perforating artery (700–800 μm) by atheromatous lesions in the vicinity of the orifice of a parent artery, leading to infarction in the entire area (cylinder-shaped) of the perforating artery **(Fig. 1)**. Being a pathological concept, BAD did not attract attention for a long time, but it has recently been garnering attention since magnetic resonance imaging has become more common. Owing to the advancement in imaging modalities, diagnostic imaging is replacing pathological concepts. Based on previous studies using imaging, following points have gained consensus regarding definition of BAD: in middle cerebral artery (MCA) perforators, infarcts with a diameter ≥ 15 mm that involve ≥ 3 or 4 axial slices on diffusion-weighted imaging; and in vertebrobasilar perforators, infarcts that reach the ventral surface of the pons (regardless of size or shape), with no stenosis (>50%) or occlusion of a major artery of the branch artery[3-23]. However, classification of diseases is complicated. In the Trial of Org IO172 in Acute Stroke Treatment (TOAST) classification,

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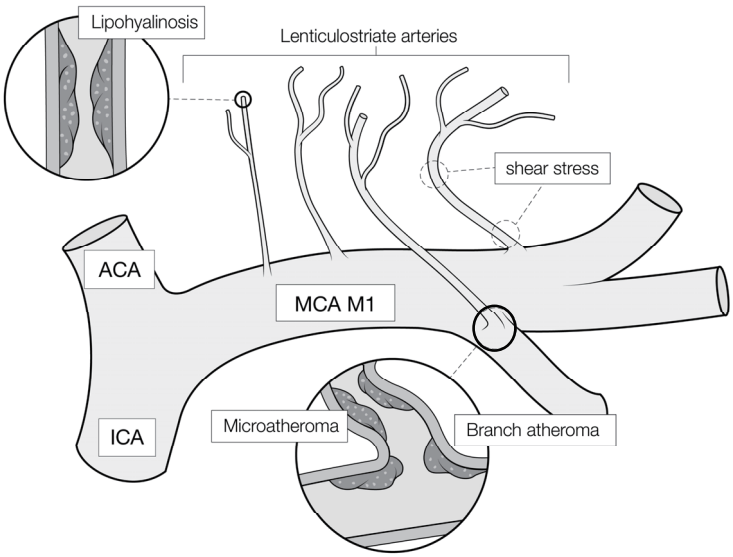

Fig. 1. Schematic diagram of a perforating branch lesions of the middle cerebral artery causing the branch atheromatous disease (BAD) or lacunar infarction

The branches of the lenticulostriate arteries (LSA) are thicker and steeply angled toward the outer side of M1 and run in the opposite direction of blood flow in M1, i.e., inward. These anatomical characteristics of LSA are based on the generation of microatheroma, leading to platelet activation by shear stress. Some LSAs may have lipohyalinosis, which causes lacunar infarction instead of BAD.
Solid circles, enlarged views of inside of the blood vessel
ACA, anterior cerebral artery; ICA, internal carotid artery; MCA M1, proximal segment of the middle cerebral artery

which is widely used for classifying cerebral infarction, there is a clear cut-off value of <15 mm for small vessel occlusion and $\geq 50\%$

stenosis or occlusive lesion in the responsible vessel for large artery atherosclerosis[24]; therefore, BAD is neither considered a large artery atherosclerosis nor a small vessel occlusion, and thus, is classified into the category of undetermined etiology. In the Stop Stroke Study (SSS)-TOAST classification[25], proposed as the revised version of TOAST classification, the maximum diameter specified for small vessel occlusion is 15–20 mm, and BAD may meet this criterion if a diagnosis of small vessel occlusion is made according to SSS-TOAST classification. However, pathologically, BAD is not a small vessel occlusion (true lacunar infarction). This may make classification of BAD more difficult and affect clinical studies and treatment strategies. Above all, the most notable factor for BAD is the very high frequency of occurrence of early neurological deterioration (END)[26]. The mechanism of END in BAD remains unclear, and a prospective study is currently ongoing to elucidate the underlying mechanism[27]. If BAD is diagnosed at admission, potent antithrombotic therapy should be promptly administered to prevent END. However, prospective large-scale randomized controlled trial with a large number of patients has not yet been conducted for the acute treatment of BAD, and no therapy with established efficacy currently exists[27]. This review article summarizes acute treatments used for BAD, especially that in the lenticulostriate artery (LSA) region, for which, many cases have been reported. The prospects for optimal treatment are also discussed.

Reperfusion Therapy

Reperfusion therapy for acute cerebral infarction comprises intravenous administration of alteplase, a recombinant tissue plasminogen activator (rt-PA), and/or mechanical thrombectomy[28]. BAD is a perforator infarction without significant stenosis of the major artery; therefore, intravenous alteplase therapy without mechanical thrombectomy is generally advised. The efficacy of intravenous alteplase therapy for acute cerebral infarction has been demonstrated in many clinical studies, regardless of the disease type of cerebral infarction[29-32]. However, to the best of our knowledge, three studies[9, 18, 19], including one of ours[9], have reported the effect of intravenous alteplase therapy on BAD **(Table 1)**. We administered alteplase (0.6 mg/kg) intravenously to treat BAD in the LSA region. Alteplase improved neurological symptoms in six of eight patients within 60 min of administration, but in four of these patients, neurological symptoms aggravated again at

Table 1. Previous reports of intravenous recombinant tissue plasminogen activator therapy for branch atheromatous disease[§]

First author, year	Study design	Perforating branch infarct location	Initial treatment, number of cases	Post-therapy	END[§§], *n* (%)	mRS ≤ 1 at 3 months, *n* (%)	sICH
Deguchi I, 2013[9]	Retrospective	LSA	rt-PA group only (0.6 mg/kg), *n*=8	5 patients received argatroban, 6 received clopidogrel/aspirin, 4 received cilostazol	No definition	4 (50 %)	1 (13%)
Park MG, 2016[18]	Retrospective	LSA	rt-PA group (0.9 mg/kg), *n*=9	75 mg of clopidogrel once daily	6 (66.7%)	2 (20%)	0
			non-rt-PA group (300 mg of clopidogrel), *n*=26	75 mg of clopidogrel once daily	18 (69.2%)	7 (29.6%)	0
Wu X, 2020[19]	Retrospective (propensity score matching)	LSA, PPA	rt-PA group (0.9 mg/kg), *n*=42	75 mg of clopidogrel and 100 mg of aspirin once daily	5 (11.9%)	28 (66.7%)	2 (5%)
			control group (300 mg of clopidogrel and 100 mg of aspirin), *n*=42	75 mg of clopidogrel and 100 mg of aspirin once daily	13 (31.0%)	14 (33.3%)	0

Abbreviations: END, early neurological deterioration; LSA, lenticulostriate artery; mRS, modified Rankin Scale; PPA, paramedian pontine artery; rt-PA, recombinant tissue-type plasminogen activator; sICH, Symptomatic intracranial hemorrhage

[§]Definitions of branch atheromatous disease

Deguchi I: Infarction involving ≥ 3 axial slices on diffusion-weighted imaging (DWI) in the lenticulostriate artery (LSA); and no stenosis (≥ 50%) or occlusion of a major artery of the branch artery and no cardioembolic source (e.g., atrial fibrillation) on magnetic resonance angiography

Park MG: Infarction involving ≥ 3 axial slices on DWI in the LSA territory; no evidences of large artery disease (>50% stenosis of relevant artery) and cardioembolism according to the classification of the Trial of Org 10172 in Acute Stroke Treatment (TOAST)

Wu X: Infarcts with a diameter ≥ 15 mm that involves ≥ 3 axial slices on DWI in the LSA territory, or lesions extending to the ventral pontine surface in the paramedian pontine artery; neither evidence of large arterial stenosis (>50%) or occlusion, nor evidence of cardiogenic embolism

[§§]Definition of END

Park MG: END was defined as an increase of ≥ 1 point in motor power or an increase of ≥ 2 points in the total National Institutes of Health Stroke Scale (NIHSS) score within 7 days after stroke.

Wu X: END was defined as an increase of ≥ 2 points in the NIHSS score within 7 days after stroke.

24 h after administration[9]. Expansion of the infarct area was observed in all patients with aggravation. Similar to our findings, Park *et al.*[18] reported that the intravenous alteplase therapy (0.9 mg/kg) administered for BAD in the LSA region failed to sufficiently prevent END and did not achieve favorable outcomes compared to the group treated with antiplatelet therapy alone[18]. In contrast, Wu *et al.*[19], who compared the alteplase group (0.9 mg/kg) with control group for BAD in the LSA region and paramedian pontine arteries using propensity score matching, reported that the incidence of END decreased and clinical outcomes were favorable in the alteplase group, concluding that alteplase administration was effective for BAD. Factors influencing the therapeutic effect of alteplase are dosage, management after administration, and posttreatment (at least 24 h after administration). Wu *et al.* also suggested that the difference in the dose of alteplase might have caused the differences in the results[19]. The results of the ENCHANTED study[33], a trial that compared two dosages of alteplase (0.6 and 0.9 mg/kg), revealed that the incidence of symptomatic intracranial hemorrhage (sICH) was low in the low dose group, but the clinical outcomes were similar between the two groups, showing no difference in efficacy between the two dosages of alteplase. However, the effect of changing the dosages of alteplase on BAD is unknown, and therefore, the relationship between the dosage of alteplase and the therapeutic effect needs elucidation in future studies. Furthermore, strict blood pressure control (systolic blood pressure <180 mmHg, diastolic blood pressure <105 mmHg) is usually required after alteplase administration to prevent bleeding complications[25]. However, we speculate that this may lead to the re-exacerbation of symptoms after alteplase administration. Many anastomoses exist at precapillary levels in the LSA[34]. Yamada *et al.* reported the importance of maintaining collateral blood flow via microcirculation coming from the neighboring LSAs to prevent the expansion of LSA territory infarcts[35]. Therefore, rapid reduction of blood pressure may reduce the blood volume in microcirculation, resulting in expansion of the infarct area. Thus, to maintain the effects of alteplase therapy for BAD, it is important to maintain hemodynamics while paying attention to excessive decrease in blood pressure. The safety and efficacy of antithrombotic drugs administered within 24 h after alteplase administration have not yet been established[28]. Therefore, at present, antithrombotic drugs are avoided within 24 h after alteplase administration. However, platelet activation has been suggested to play an important role in the initial

neurological progression of BAD[2]. Inhibition of platelets is important to maintain blood flow through a branch with small diameter in patients with BAD treated with alteplase[18]. To prevent re-exacerbation of symptoms after alteplase administration, it is necessary to consider parallel administration of antiplatelet agents from the early stage of treatment (within 24 h). Furthermore, posttreatment after alteplase administration is also important. In a study by Wu *et al.*[19], which demonstrated the efficacy of alteplase, dual-antiplatelet treatment (DAPT) with clopidogrel and aspirin was administered as posttreatment after alteplase. In contrast, Park *et al.*[18] used clopidogrel monotherapy as posttreatment after alteplase, but the efficacy of alteplase was not observed in this study[18]. Seven of nine patients showed improvement in neurological symptoms at 24 h after alteplase administration, but four among seven patients showed reaggravation after improvement. As described above, differences in posttreatment might have affected clinical outcomes. Furthermore, it has recently been reported that the efficacy of acute treatment with DAPT without alteplase was equivalent to that with alteplase alone in cases of minor stroke[36]. The efficacy of alteplase in BAD needs to be investigated in a larger number of patients to determine the dosage, management after administration, and posttreatment. Another report suggested that the administration of tirofiban (GPIIb/IIIa receptor antagonist), a platelet aggregation inhibitor, for BAD after intravenous infusion of urokinase significantly inhibited END compared with the administration of urokinase alone[23]. Recently, tenecteplase, which has a longer half-life and a higher fibrin specificity than alteplase, has been drawing attention as an alternative to alteplase[37]. The treatment results showing the effect of tenecteplase on BAD are awaited.

Antiplatelet Therapy

Since the pathology of BAD is non-cardiogenic cerebral infarction caused by arteriosclerosis, antiplatelet therapy is the mainstay treatment. The LSA is a perforating branch of the main trunk of the MCA (M1), consisting of 2–12 vessels (average, 7.1 vessels) and branches from the superior or posterior surface of M1 measuring 2–14.9 mm from the M1 origin[38-40]. Proximal to the M1, the caliber of the vessel is small. The outermost proximal portion measures 700–800 μm. In the common trunk, the caliber may exceed 1 mm[41, 42]. Importantly, the branches of the LSA are steeply angled toward the outer side of M1 and run in the opposite direction of blood flow in M1, i.e., inward **(Fig. 1)**. This may be an adaptation to pressure loading[41, 43, 44]. Under edaravone administration, cilostazol has been reported to be effective in paramedian pontine artery infarcts, while clopidogrel has shown efficacy in LSA region infarcts. The reason for this is unclear, but owing to a greater inhibitory effect on platelet aggregation under shear stress **(Fig. 1)**, clopidogrel may be more effective in the LSA region, which has a large diameter of 700–800 μm immediately after bifurcation and runs in a retrograde fashion[45, 46]. The use of more potent antiplatelet agents may be effective in inhibiting the progression of BAD in the LSA region. In lacunar infarcts, which have foci similar to cerebral infarction, the use of more potent antiplatelet therapy may outweigh concerns about hemorrhagic complications, although caution is warranted in BAD because lipohyalinosis in the peripheral perforating branch poses a risk of cerebral hemorrhage concurrent with infarction **(Fig. 1)**.

In this regard, DAPT is generally advised. The efficacy of acute DAPT for non-cardiogenic cerebral infarction has been demonstrated in large-scale clinical studies[47, 48]. Moreover, guidelines[28] strongly recommend 21 days of DAPT with aspirin and clopidogrel within 24 h after the onset of symptoms in patients with non-cardiogenic cerebral infarction who did not receive intravenous alteplase therapy. The authors propose that the following aspects of DAPT should be considered for the treatment of BAD: (1) presence or absence of a loading dose, and (2) combination of DAPT. Regarding the loading dose, an initial dose of 300 mg of clopidogrel loading (CL) was approved in Japan in 2018 for preventing the recurrence of acute non-cardiogenic cerebral infarction. Clopidogrel is a prodrug and is metabolized in vivo in two steps by cytochrome P450, a hepatic metabolic enzyme, thereby leading to a delay in the onset of action, unlike aspirin. However, this delay can be reduced by the first CL dose[49]. Several studies have elucidated the efficacy of first CL administration for BAD. Ikeda-Sakai *et al.*[20] compared the CL group (300 mg on day 1, followed by 50–75 mg once daily) with non-loading (NL) group (50–75 mg once daily) for acute cerebral infarction. The results revealed that the CL group had a higher proportion of patients with END within 48 h after admission than the NL group and that CL was not effective for BAD. However, concomitant use of other antithrombotic drugs (oral/intravenous antithrombotics) was not standardized in both groups, and the possibility that drugs other than CL affected the results cannot be ruled out. We also investigated the effect of CL on BAD by comparing a group of patients who received the conventional multiple antithrombotic therapy (aspirin + clopidogrel + argatroban) with a group that received the therapy

combined with CL[10]. The results showed that CL combined with multiple antithrombotic therapy significantly inhibited acute END, especially, the worsening of movement symptoms, compared to multiple antithrombotic therapy alone. However, these studies were retrospective, and a prospective study including a large number of patients is warranted to elucidate the effect of CL on BAD. Furthermore, DAPT, including cilostazol, is effective for BAD. Kimura *et al.*[21] conducted a multicenter prospective study to elucidate the effect of DAPT including cilostazol (cilostazol plus aspirin or cilostazol plus clopidogrel) from the very early stage and antiplatelet monotherapy for patients with BAD, and reported that DAPT including cilostazol showed significant suppression of acute progressive motor paralysis[21]. In addition, Yamamoto *et al.* reported that combination therapy with cilostazol and clopidogrel improved the functional prognosis in patients with BAD, especially in the LSA region[45]. Another study compared the combination of aspirin and cilostazol with aspirin alone in patients with non-cardioembolic ischemic stroke administered within 48 h after the onset of stroke, and reported that aspirin plus cilostazol significantly inhibited the exacerbation of neurological symptoms within 14 days after the onset as compared to aspirin alone[50]. A study, not conducted in patients with BAD, showed that combination therapy with aspirin and ticagrelor, which is a direct and reversible P2Y12 receptor antagonist, in patients with mild-to-moderate acute non-cardioembolic ischemic stroke resulted in a lower risk of the composite of stroke and death within 30 days compared with aspirin alone[51]. However, severe bleeding increased with ticagrelor. The third-generation thienopyridines and the prodrug prasugrel, which have shown efficacy and safety comparable to clopidogrel, are also the potential candidates for DAPT[52]. It has been suggested that prasugrel may have differences in efficacy depending on the types of stroke[53]. The safety concerns for hemorrhage when prasugrel is used for stroke in combination with aspirin should be kept in mind. In the future, an optimal combination of antiplatelet agents may be discovered by studying patients treated for BAD with various combinations of antiplatelet agents.

Anticoagulation Therapy

Fibrin thrombus is also considered to be involved in the mechanism of BAD progression. Significant increases in coagulation and fibrinolysis activation, in addition to platelet function, have been demonstrated in patients with progressive cerebral infarction or those with large lacunar infarct areas[54]. Therefore, besides antiplatelet agents, anticoagulants are also prescribed in clinical practice for treating BAD. In particular, argatroban is prescribed in combination with antiplatelet agents for approximately 80% of patients with BAD in Japan[55]. Argatroban selectively inhibits thrombin and, thus, suppresses thrombin-induced fibrin formation, platelet aggregation, and vasoconstrictive action[56, 57]. However, there is an increased risk of bleeding. Concomitant use of anticoagulants and antiplatelet agents is known to increase the risk of bleeding[58]. Particularly, since DAPT is used for BAD, increase in the risk of bleeding is heightened. However, both in our study, wherein argatroban was used in combination with aspirin and clopidogrel in all patients, and in a study by Kimura *et al.*, wherein argatroban was used in combination with cilostazol and aspirin or clopidogrel in 76.8% of patients, no cases of sICH or systemic hemodynamics were observed[10, 21]. The results of a meta-analysis also showed that argatroban significantly improved neurological functions in patients with cerebral infarction and reduced the incidence of early neurological worsening, but did not increase bleeding events (symptomatic/asymptomatic intracranial hemorrhage, gastrointestinal bleeding, and major systemic hemorrhage)[59]. Therefore, argatroban is considered a highly safe drug when used in combination with DAPT.

Although evidence for the efficacy of argatroban in BAD is lacking, our results suggest the presence of a hemodynamic component in the pathogenesis of BAD, and anticoagulation therapy may be effective in addition to antiplatelet therapy[10]. In particular, the combination of other types of anticoagulants having less bleeding complications with antiplatelet agents may be promising. Therefore, factor XI inhibitors, which are important for thrombus formation but have little role in hemostasis, are being developed **(Table 2)**[60, 61]. The mechanisms of these drugs have led to the development of candidates listed in the table, and the results of phase II clinical trials using milvexian and asundexian as small molecules for the prevention of progression and recurrence of acute cerebral infarction have been published and presented, but further validation of the effectiveness is awaited[62]. Although the efficacy of factor XI inhibitors in BAD is unknown currently, but they are speculated to be a potential candidate for combination therapy with antiplatelet agents in the future.

Other Drugs

Besides antithrombotic drugs, statins with pleiotropic effects (anti-inflammatory activity, enhanced endothelial function, inhibition of oxidative

Table 2. Factor XI (a) inhibitors for thrombosis[§]

	Small molecules	Monoclonal antibodies	Aptamers	Antisense oligonucleotides	Natural inhibitors
Mechanism of action	Direct inhibition of FXIa	Direct inhibition of FXI/FXIa	Direct inhibition of FXIa	Inhibition of FXI biosynthesis	Direct inhibition of FXIa
Route of administration	IV or Oral	IV or SC	IV or SC	SC	IV
Dosing	Daily	Monthly	Daily	Weekly	Daily
Onset of action	Minutes/Hours	Hours	Minutes/Hours	Weeks	Minutes
Offset of action	Minutes/Hours	Weeks	Minutes/Hours	Weeks	Hours
Medication name	Asundexian	Osocimab	FELIAP	ISIS-FXIRx	Fasxiator
	Milvexian	Abelacimab	29 nt 11.16	Fesomersen	Ir-CPI
	ONO-7684	Xisomab	40-nt 12.7		
		MK-2060			

Abbreviations: IV, intravenous; SC, subcutaneous
[§]Table 2 adapted from [61].

stress, etc.) are expected to be effective drugs for BAD[63]. A systematic review showed that a higher dose of statins for ischemic stroke, beginning from the acute phase, significantly reduced the National Institutes of Health Stroke Scale score and improved the short-term functional outcome without increasing adverse events[64]. A prospective study[22] aimed to evaluate the effect of statins, administered within 24 h of onset, on END and recurrent stroke in patients with BAD is currently ongoing. The study plans to compare the intervention group in which DAPT (aspirin + clopidogrel) along with high-intensity statins is administered with the historical control group. The results of the study are awaited.

Combined use of a free radical scavenger (edaravone) may also be effective in preventing nerve cell and vascular endothelial cell damage caused by free radical production attributable to cerebral ischemia[65]. In a systematic review, the results of three randomized controlled trials covering a relatively small number of patients (496 patients) were analyzed in a consolidated manner, and the administration of edaravone was shown to improve neurological outcomes[66]. In Japan, edaravone is commonly administered to patients with acute ischemic cerebral infarction and it has also been used in combination in 72.8% of patients with BAD[55]. It is important to prevent the progression and expansion of infarct areas including white matter and damage to the corticospinal tract in BAD. White matter is characterized by high lipid content and is susceptible to damage by free radicals[67]. Although the efficacy of free radical scavengers in the treatment of BAD is currently unclear, their administration is considered significant to prevent white matter disorder.

Conclusions and Prospects

This review article focused on the acute treatment of BAD. In monotherapy for BAD, there are limitations in the improvement of progressive exacerbation and functional prognosis, and at present, using aggressive therapeutic intervention, mainly comprising antiplatelet therapy (DAPT) in combination with anticoagulant therapy (argatroban), free radical scavengers, and statins, for the hyperacute phase is desirable. Indeed, administration of rt-PA intravenous therapy (alteplase) achieves a certain level of efficacy; however, some issues, such as dosage, management after administration, and posttreatment, to enhance the efficacy are unresolved. Although it is an important disease in clinical practice, the current concept of BAD is not sufficiently used in clinical practice and research in Western countries. It is a matter of great concern that BAD, which has a completely different mechanism, has been generally categorized as an embolic stroke of undetermined source in large-scale clinical studies[68]. It is necessary to start by categorizing BAD as a type of cerebral infarction based on a clear definition. We hope that this review article will contribute to the elucidation of its pathology and establishment of optimal treatment methods.

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Conflicts of Interest

The authors declare that no conflicts of interest exist.

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