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Cerebral border zone infarctions: An etiologic study

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Mazyar Hashemilar[1,2], Parla Tohidi[1,2], Nasrin Forghani[1,2], Elyar Sadeghi-Hokmabadi[1,2], Ehsan Sharifipour[3]

[1] Neurosciences Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2] Department of Neurology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[3] Neuroscience Research Center, Qom University of Medical Sciences, Qom, Iran

Keywords
Stroke; Cerebral Infarction; Causality; Intracranial Embolism; Atherosclerosis; Brain Infarction

Abstract

Background: Cerebral border zone infarctions (BZIs) are a subtype of acute ischemic stroke that occur at the junction between two major cerebral arterial territories. Internal and external BZIs are defined based on the known patterns in brain magnetic resonance imaging (MRI). However, the etiology and pathophysiology of these two types of BZI are still debated. This study aimed to determine the etiologic differences of two types of BZI to guide tailor appropriate treatment strategies for these patients.

Methods: In this prospective study, patients with BZIs were enrolled from patients with acute ischemic stroke admitted to the hospitals affiliated with Tabriz University of Medical Sciences, Tabriz, Iran, from 2017 to 2019. Appropriate clinical and laboratory workups were applied to determine possible etiologies of ischemic stroke according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system.

Results: The study included 106 patients with BZI, 53 patients in each group. Both types of BZI were more frequent in males. However, there was no significant difference between the two types concerning sex, age, and profile of major stroke risk factors. The results showed no correlation between the type of BZI and hemodynamic factors (P = 0.086). However, large artery atherosclerosis (LAA) was the most frequent etiology within each subtype of BZI; LAA in internal (P = 0.016) and cardioembolism (P = 0.046) in external BZI were more frequent etiologic subtypes of cerebral infarction.

Conclusion: LAA might be the most common etiology for internal and external cerebral BZIs. Cardioembolism might have a more important etiologic role in the external subtype.

Introduction

The concept of border zone infarction (BZI) was first discussed in the 19th century.[1] Zulch and Behrend reported typical BZI topographic areas and hypothesized about their hemodynamic mechanisms.[2]

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Corresponding Author: Mazyar Hashemilar
Email: mhashemilar@yahoo.com

BZIs are ischemic lesions located at the junction between two arterial territories and account for about 10% of all brain infarctions.[3] The terms BZI and watershed infarctions are used interchangeably, and we preferred the former term.

The imaging characteristics of BZIs have already been discussed and classified.[4,5] Two separate supratentorial watershed areas are described: superficial and deep (Figure 1). 'Superficial,' 'cortical,' or 'external' BZIs are located between the cortical territories of the middle cerebral artery (MCA) and either anterior or posterior cerebral arteries. The 'deep' or internal BZIs are located between the MCA deep branches and superficial arterial systems.[4]

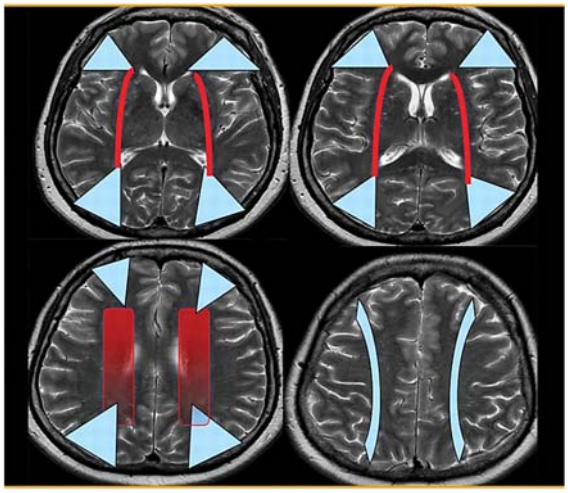

Figure 1. Color depiction on axial T2-weighted magnetic resonance imaging (MRI) of normal brain showing approximate locations of external (blue) and internal (red) border zone infarcts (Adopted from Mangla et al.[4])

The etiology of BZI is still under investigation. However, some studies suggest that internal BZIs are due to hemodynamic compromise secondary to proximal stenosis and/or hypoperfusion due to low cardiac output. In contrast, cortical BZI has been suggested to be induced by embolization from the heart or atherosclerotic plaques in large arteries.[6] Brain collateral circulation plays an essential role in protecting against BZI development by maintaining adequate cerebral perfusion by redistributing ischemic areas. The circle of Willis is a major source of collateral flow, but its anomalies usually affect its ability to maintain adequate perfusion, increasing the risk of BZI.[3] The treatment of patients with cerebral infarction is based on the pathophysiology of the lesion. Knowledge about the possible causative mechanisms of BZIs leads to a more reasonable selection of appropriate treatment modalities by clinicians. This study aimed to clarify the cause of this type of cerebral infarction for better decision-making about the treatment options.

Materials and Methods

We designed a prospective study recruiting 106 patients clinically diagnosed with acute ischemic stroke with magnetic resonance imaging (MRI) confirmation of either external or internal BZI from the beginning of 2017 to the end of 2019. These patients were admitted to the neurology in-patient facilities of hospitals affiliated with Tabriz University of Medical Sciences, Tabriz, Iran, and diagnosed with acute ischemic stroke by an experienced neurologist (MH) and a vascular neurologist (ESH). They were evaluated for inclusion in the study, and eligible patients were included. The major risk factors for stroke were determined in both internal and external BZI groups, which included hypertension, diabetes mellitus (DM), smoking, hyperlipidemia, history of transient ischemic attacks or stroke or myocardial infarction (MI), and history of heart disease, including mitral valvular disease, atrial fibrillation, and heart failure. Definitions for hypertension, DM, smoking, and hyperlipidemia were based on 2019 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines.[7] The primary outcome of the study was to reach a probable etiology for either type of BZI using the available diagnostic workups. The inclusion criteria consisted of a diagnosis of acute ischemic stroke, a brain MRI pattern of BZI using appropriate sequences, especially diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC) sequences, according to defined patterns,[4] either internal or external BZI. The old silent or symptomatic infarcts of either BZI pattern or territorial infarcts were excluded. The other exclusion criterion was acute infarcts in the territory of specific arteries, MCA, ACA, and posterior cerebral artery (PCA). All the concomitant BZI and territorial infarcts were also excluded from the study. BZIs were divided into two groups: external (n = 53) and internal (n = 53). Vascular imaging studies, including extracranial cervical vessels duplex study, transcranial Doppler (TCD), cervical magnetic resonance angiography (MRA), computed tomography angiography (CTA), or digital subtraction angiography (DSA) of both cervical and intracranial vessels, were performed on

the patients. An extracranial cervical vessels duplex study, TCD, was performed for all patients. The most common vascular imaging modality we used was MRA. Only 33 out of 106 patients underwent CTA, and 12 were studied with DSA.

Transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), in-patient continuous electrocardiographic monitoring, and/or 72-hour ambulatory Holter monitoring were performed to evaluate possible sources of cardiac embolism. The left atrial diameter (LAD) was determined by measuring the one-dimensional anteroposterior (AP) M-mode of the LAD using TTE, performed and interpreted by an experienced cardiologist.

The relationship between BZIs and hemodynamic factors was evaluated based on the conditions predisposing to hypotension at the onset of symptoms, considering the patient's history and clinical context. The findings in patients' history in favor of hemodynamic compromise included a history of syncope or presyncopal symptoms (paleness, sweating, and palpitations), history of recurrent episodes of orthostatic dizziness, contributed by the patient himself or a witness, and an episode of verified overtreatment and lowering of blood pressure.

After performing the above-mentioned diagnostic tests, the obtained etiologies were matched to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (Table 1).[8] In the TOAST classification, LAA is defined as patients with cerebral infarcts who have clinical and cerebral imaging findings of either significant (> 50%) stenosis or occlusion of a major brain artery or cortical branch artery, presumably due to atherosclerosis.[8] Congestive heart failure (CHF) is defined as a clinical syndrome in which symptoms result from a structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.[9] The cases with an ejection fraction of < 15% were included in the study.

Table 1. Trial of Org 10172 in Acute Stroke Treatment (TOAST) Classification of subtypes of acute ischemic stroke

LAA (embolus/thrombosis)*
Cardioembolism (high-risk/medium-risk)*
Small-vessel occlusion (lacune)*
Stroke of other determined etiology*
Stroke of undetermined etiology
a. Two or more causes identified
b. Negative evaluation
c. Incomplete evaluation

LAA: Large artery atherosclerosis
Adopted from Trial of Org 10172 in Acute Stroke Treatment (TOAST).[8]
*Possible or probable, depending on the results of ancillary studies

This study was approved by the Ethics Committee of Tabriz University of Medical Sciences (approval code: 94/3-6/9). Statistical analysis of the data was performed using the SPSS software (version 24, IBM Corporation, Armonk, NY, USA). Group statistics were expressed as mean and standard deviation (SD) for categorical variables and percentages for descriptive analysis. The chi-squared and or Fisher's exact tests were used to compare the categorical variables and the student's t-test for continuous variables. $P \leq 0.050$ was considered significant in all statistical analyses.

Results

Totally, 106 patients were enrolled. The demographic characteristics and profile of major stroke risk factors of the patients in both internal and external BZI are shown in table 2.

Although the odds ratio of both internal and external BZI was higher in men than women, this difference was not statistically significant (P = 0.193 and P = 0.187 in men and women, respectively).

Table 2. The profile of the major stroke risk factors in patients with border zone infarction (BZI)

Risk factor	Internal BZI	External BZI	P
Age (years) mean (Range)	69.68 (49-91)	68.01 (24-93)	0.118
Sex [n (%)]			
Female	16 (30.2)	21 (39.7)	0.193
Male	37 (69.8)	32 (60.3)	0.187
Hypertension* [n (%)]	32 (60.4)	39 (73.6)	0.148
DM* [n (%)]	15 28.3)	15 (28.3)	> 0.999
Smoking [n (%)]	15 (28.3)	9 (17.0)	0.164
Hyperlipidemia* [n (%)]	9 (17.0)	5 (9.4)	0.251
H/O TIA/Stroke/MI [n (%)]	20 (37.7)	17 (32.1)	0.541

*Definition based on 2019 American College of Cardiology/American Heart Association (ACC/AHA) guidelines
BZI: Border zone infarction; H/O: History of; MI: Myocardial infarction; TIA: Transient ischemic attack; DM: Diabetes mellitus

The mean ages in the internal and external BZI groups were not significantly different (P = 0.118). Our study showed no statistically significant differences with regard to the major stroke risk factors between the external and internal BZI groups.

The relationship between BZIs and hemodynamic factors was evaluated based on the conditions predisposing to hypotension at the onset of symptoms based on the patient's history and clinical status. In the external BZI group, three patients had syncope and marked hypotension before the ischemic stroke, and one patient had an ischemic stroke following hypotension during dialysis. Based on patient history and clinical context, 4 (7.54%) patients had marked hemodynamic instability before the external BZI. In the internal BZI group, 3 (5.66%) patients had marked hypotension before the ischemic stroke. The results showed no correlation between the type of BZI and hemodynamic factors (P = 0.068). Table 3 presents the etiologic subtypes of BZIs separately for internal and external groups based on the TOAST classification.[7] In the present study, within each type of BZI, LAA was the most frequent etiologic subtype (P = 0.005). However, a comparison of the etiologic subtypes between the two types of BZI proved that LAA in the internal (P = 0.016) and cardioembolism (P = 0.046) in the external BZI were more frequent etiologic subtypes of cerebral infarction.

In the external BZI group, two patients were included in the "stroke of other determined etiology" category of the TOAST classification (Table 3). One of these patients was a 24-year-old woman diagnosed with Behcet's disease, and the other was a 27-year-old woman diagnosed with afibrinogenemia. In the undetermined etiologic group with 19 cases, in 18 patients, the clear etiology of infarction was not determined despite the studies performed. In one patient in this group, two simultaneous etiologies, atrial fibrillation (AF) and large artery atherosclerosis (LAA), were found. The LAD levels were measured using echocardiography in three etiologic subtypes of LAA, cardioembolic etiology, and undetermined etiology group. The mean LADs measured in patients with LAA, cardioembolic etiology, and undetermined etiology were 3.49, 4.39, and 3.32 cm, respectively. As shown in table 3, the mean LAD in "the cardioembolic category" of our cases was significantly higher than "the stroke of other determined etiology category" of the TOAST classification (P = 0.046).

Discussion

The age and sex of patients with ischemic infarcts are known as the major and non-modifiable risk factors of stroke. In this study, there was no statistically significant relationship between the age and sex of patients in any of the external or internal BZIs. The other risk factors of stroke also showed no significant differences between the two groups (Table 2). These findings are consistent with studies that also found no association between these risk factors in BZIs.[10,11]

The traditional concept about the pathogenesis of BZI has been a hemodynamic compromise attributable to severe stenosis in large arteries or acute hypotensive events, such as cardiopulmonary bypass.[12] Many studies on the pathogenesis of BZI have supported this theory based on findings such as frequent and severe arterial stenosis in patients with BZI, increased regional oxygen extraction, decreased regional cerebral blood flow on positron emission tomography (PET), and other evidence through carotid Doppler imaging, MR perfusion, or MR spectroscopy.[11-19] In the present study, within each type of BZI, LAA was the most frequent etiologic subtype (Table 3), consistent with previous studies. The association between carotid artery occlusive disease and internal BZIs has been demonstrated in many studies.[20,21]

Table 3. Etiologic subtypes of cerebral internal and external border zone infarction (BZI)

TOAST classification [n (%)]	**Internal BZI** (n = 53)	**External BZI** (n = 53)	**P**
LAA	28 (52.8)	22 (41.5)	0.016
Cardioembolism	6 (11.3)*	10 (18.9)**	0.046
Stroke of undetermined etiology	19 (35.9)	19 (35.8)	-
Stroke of other determined etiology	0 (0.0)	2 (3.8)	0.500

*High risk: Five patients with atrial fibrillation (AF) only and one patient with AF associated with congestive heart failure (CHF) with ejection fraction (EF) < 15%.

**High risk: Seven patients with AF only, one patient with AF associated with severe mitral stenosis and CHF with

EF < 15%, one patient with AF and CHF (EF < 15%); Medium risk: one patient with CHF (EF < 15%).

BZI: Border zone infarction; LAA: Large artery atherosclerosis; TOAST: Trial of Org 10172 in Acute Stroke Treatment[8]

El-Gammal et al. examined intra- and extracranial arteries in patients with BZIs. In their study, patients with cortical watershed infarction had a lower rate of vascular stenosis; i.e., CT angiography did not show a significant difference in the rate of large vessel stenosis in the external watershed infarction group compared to the control group.[22] In a study by Dong et al., vascular risk factors in patients with BZI were evaluated.[23] In the internal BZI group, there was a higher degree of stenosis or obstruction of MCA and carotid arteries on the same side and MCA on the opposite side compared to the non-watershed infarction group, with no significant difference in stenosis or obstruction of large arteries compared to the non-watershed infarction group. A study by Sorgun et al. also showed that internal BZIs are more likely to be caused by LAA, and LAA is significantly associated with internal BZIs.[24]

It is speculated that in addition to hypoperfusion, arterial embolism is also a triggering factor in the production of BZIs in patients with ICA obstruction.[25,26] Caplan and Hennerici demonstrated this hypothesis by reporting the case of a patient with severe internal carotid artery stenosis in which DWI showed a series of small round lesions in the subcortical region bilaterally, and TCD recorded microembolic signals in bilateral MCA.[26] The present study showed no correlation between the type of BZI and hemodynamic factors. We believe that this inconsistency between the studies mentioned above and this study stems from the inadequacy of our methods to assess systemic hemodynamic compromise (i.e., using only historical clinical data and not objective measures such as tilt table test).

Cadioembolism is another presumed etiology of BZ. Bergui et al. examined silent cerebral infarctions. Given this study, cortical watershed areas are susceptible to microembolisms that occur during atrial fibrillation.[25] In the present study, the cardioembolic etiology was not the most common etiology of the cortical BZI, and it was shown only in 18.9% of the patients with cortical BZI. AF rhythm (Table 3) was more frequent as cardioembolic etiology in external versus internal BZI (P = 0.046). After LAA, cardioembolism was the second most frequent etiology of determined etiologies of BZI in the present study. Lack of extended and preferentially telemetric cardiac Holter monitoring in many patients studied in this study could explain the higher rate of undetermined etiology and the low incidence of cardioembolic cases in the external BZI group compared to similar studies. In the present study, no significant difference was observed in the amount of LAD measured in the LAA and undetermined etiology groups. However, in the cardioembolic group, the LAD level was significantly higher than in the two other groups, which was similar to the results of the study conducted by Jordan et al.,[27] which used the left atrial volume index (LAVI) instead of LAD to assess the size of the left atrium. Considering this study, there was no significant difference between the level of LAVI in the embolic stroke of the undetermined source (ESUS) group and the non-cardioembolic (NCE) stroke of the determined mechanism group (non-cardioembolic stroke). However, the level of LAVI in the cardioembolic group was significantly higher. Additionally, 99 patients in the ESUS group underwent continuous cardiac monitoring, 18.2% of whom had AF rhythm. The LAVI levels were significantly higher in patients with AF rhythm than without AF rhythm.[27] These findings suggest that the ESUS patients with significant left atrial enlargement might benefit from anticoagulant therapy; however, further studies are necessary. Some studies have suggested an embolic etiology for internal BZI. There is a weak association between cortical watershed infarction and hemodynamic dysfunction compared to internal watershed infarction.[28]

Several limitations of the present study should be acknowledged. First, our judgment about the relationship between the hemodynamic factors and BZIs was based on the patient's history and clinical context. Second, the patients' hemodynamic status was stabilized early on admission to the emergency department and before transfer to the neurology department. Therefore, orthostatic blood pressure measurement change was not a reliable indicator in our patients. The best method to make a sound judgment about the association between the hemodynamic factors and BZI is through the quantitative measurement of cerebral blood flow or demonstrating an apparent decrease in cerebral perfusion pressure. Finally, since a high percentage of the patients in this study were in the undetermined etiology group, it is suggested that long-term, preferentially telemetric Holter monitoring be performed to find possible AF rhythms in all the patients with BZIs.

Conclusion

In this study, LAA was the most common etiology for infarction in both internal and external BZI groups. However, LAA in the internal and cardioembolism in the external BZI were significantly more frequent etiologies, respectively.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

None.

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