Original Article

Etiopathology, Clinical and Imaging Characteristics of Border Zone Strokes

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Abstract

Introduction: A border zone infarct (BI) is defined as an infarction that is localized to watersheds or border zones in the brain. BI is further classified into cortical border zone infarct (CBZ) and internal border zone infarct (IBZ). This study was conducted to explore the clinical and radiological characteristics of BI. **Materials and Method:** The study was conducted on eligible 400 acute ischemic stroke patients out of which 52 BI patients (diagnosed by the radiologist on DWI MRI images), patients >18 yrs of age were selected and divided into two groups of IBZ and CBZ infarct patients. The degree of intracranial and extracranial stenosis and characteristics on clinical presentation were assessed. The data were collected and analyzed using SPSS version 20.0 software at significance level p-value <0.05. **Results:** 25% and 75% of CBZ and IBZ patients, respectively, had history of presyncope or syncope before stroke. On vascular evaluation, 3.9% and 51.9% were in MCA and ICA stenosis group, respectively. Evidence of cardio embolism was found in 17.3% of patients. 53.3% of CBZ and 53.8% of IBZ patients were in ICA stenosis group, and 6.7% of CBZ and 7.7% of IBZ patients were in MCA stenosis group, with a statistically insignificant relation (p-value >0.05). **Conclusion:** Association of BI with events causing hypotension or hypovolemia is well-established in our study, association of BI with large vessel atherosclerosis is common, and its contribution to CBZ and IBZ seems to be equal.

Keywords: Border- zone infarct, cortical border zone infarct, internal border zone infarct, stenosis

Introduction

Watersheds or border zones are defined as areas in the brain at the junction of the defined boundaries between two different non-anastomosing arterial systems.[1] A border zone infarct (BI) or watershed stroke or watershed infarct is defined as an infarction that is localized to these border zones. BI is further classified into two main categories, based on their location as cortical border zone infarct (CBZ; junctional or external border zone) and internal border zone infarct (IBZ; internal junctional or subcortical border zone).[2] BI in the cerebellum is usually less than 2 cm in size and is seen at the borders of the anterior inferior cerebellar, superior cerebellar and posterior inferior cerebellar arteries, and their branches.[2]

In many autopsy series,[3,4] BI accounts for 10% of the total brain infarcts. BI may be better explained by considering the combination of two interrelated processes: hypoperfusion and embolization. External, cortical border zone infarcts are usually wedge-shaped or ovoid. Internal, subcortical border zone infarcts appear in multiples, in a rosary-like pattern. The main goals of neuroimaging in patients with BI are to determine whether hemodynamic impairment (HDI) is present and to assess its severity. Various imaging modalities have been used to visualize perfusion in border zones and to identify the pathophysiology of border zone infarcts.[2,5,6] But still there is a lack of clarity in pathophysiology, which precludes proper and complete management of these infarcts. This is perhaps due to few previous studies using DWI imaging and/or including both IBZ and CBZ simultaneously.[2] Consequently, it is obvious that BI is still an understudied and grey area in neurology, even in the basic aspects of its clinical and radiological profiles. Thus, the main aim of the present study was to explore the clinical and radiological characteristics of BI and its etiopathology with internal comparisons between IBZ and CBZ infarcts.

Materials and Methods

The study was conducted on eligible 400 AIS patients presenting consecutively during the study period to the Department of Neurology from September 2016 to April 2018. From the study population, all 52 BI patients (diagnosed by radiologist on DWI MRI images), patients >18 yrs of age were selected and divided in an equal group of IBZ and CBZ infarcts patients. The target population was all patients of ischemic stroke. A written informed consent from the patient/legal guardian and institutional ethical clearance was taken before the initiation of research work from the institutional ethics committee. All eligible patients were approached by the

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investigator himself and were explained the nature and purpose of the study. After a detailed history and clinical examination, all the patients were subjected to MRI brain (3T) screening with DWI and FLAIR images with ADC images and CT angioneck vessels and carotid Doppler.

Presence of small cortical infarcts and potential sources of cardioembolism (PSCE) were examined to evaluate the frequency of concomitant embolic signals. Extracranial and intracranial vascular status was evaluated, and the degree of stenosis was measured and graded as being no stenosis (0% stenosis), mild (<50% stenosis), moderate (50–74% stenosis), severe (75–99%), or occluded by CT angiography and/or arterial doppler.[7] Patients without PSCE were classified as (1) no significant stenosis (those with <50% stenosis in both internal carotid artery and middle cranial artery); (2) ICA stenosis group (≥50% stenosis on ICA); and (3) MCA stenosis group (<50% stenosis in ICA and ≥50% stenosis on MCA). The radiologists were blinded about the DWI MRI findings of the patients in which they were defining degree of intracranial and extracranial stenosis. Characteristics on clinical presentation were assessed. The data were collected and analyzed using SPSS version 20.0 software, and data were considered significant if p-value <0.05.

Results

In the present study, a total of 52 (13%) BI patients out of 400 patients with ischemic strokes were enrolled. Out of 52 patients, 32 patients (62%) had CBZ and 20 patients (38%) had IBZ. Twenty-one patients (40.4%) were females, and 30 patients (59.6%) were males, with mean age 65.02 ± 15.57 years as given in Tables 1 and 2. Among CBZ patients, 13 patients (40.6%) were female and 19 patients (59.4%) were male; and among IBZ patients, eight patients (40%) were female and 12 patients (60%) were males. Mean age was 65.9 ± 16.41 and 63.5 ± 14.4 years in CBZ and IBZ, respectively. Thirty-six patients (69.2%) showed symptom progression with median duration being 371.9 ± 782.5 minutes. Thirty patients (25%) had history of presyncope or syncope, 30 patients (57.7%) had hypotension or hypovolemia, and most of the patients had diarrheal illness before stroke. Postural hypotension was found in nine cases (17.3%).

25% and 75% of CBZ and IBZ patients, respectively, had history of presyncope or syncope before stroke. 71.9% and 35% CBZ and IBZ patients, respectively, had history of hypotension or hypovolemia, with a statistically significant (p <0.05) difference. 12.5% and 25% of CBZ and IBZ patients, respectively, had a history of TIA, with an insignificant difference statistically. Hypertension and diabetes were more common in IBZ patients, but the difference was statistically insignificant. 25% of CBZ and 45% of IBZ patients were smokers, with insignificant differences statistically. 14.3% of CBZ patients showed postural hypotension. On MRI, 21.1% had bilateral involvement, and 28.8% had small cortical infarcts. On vascular evaluation, 3.9% and 51.9% were in MCA and ICA stenosis group, respectively, while 42.3% patients did not have significant stenosis in either vessel. 17.3% of patients had critical ICA stenosis. Evidence cardioembolism (PSCE) was found in 17.3% of patients. Median hospital stay was 4.5 days.

Table 1: Demographic and clinical profile of border zone infarct patients

Variable	N	Percentage
Gender		
Female	21	40.4
Male	31	59.6
Duration of progression		
No progression (<30 mins)	16	30.8
Progression (>30 mins)	36	69.2
Presence of presyncope/syncope	13	25
H/S/O prior hypotension/hypovolemia	30	57.7
H/O hypertension	35	67.3
H/O diabetes	20	38.5
H/O TIA	9	17.3
Smoker	17	32.7
Postural hypotension	4	8.3
Side of involvement on		
MRI—bilateral	11	21.2
Unilateral	41	78.8
Significant artery stenosis—		
No significant stenosis	22	42.3
ICA stenosis group	27	51.9
/MCA stenosis group	3	3.9
Critical ICA stenosis (>75%)	9	17.3
Small cortical infract	16	30.76
PSCE	9	17.3

Table 2: Demographic and clinical profile of border zone infarct patients

Variable	Mean	Std. Deviation	Median	Range
Age (years)	65.02	15.57	65	18–93
Symptom progression (min)	371.9	782.5	62.5	0–4320
Power in the weakest muscle group (MRS)	2.71	1.76	3	0–5
mRS at admission	3.08	1.40	4	1–5
mRS on Day 3	2.62	1.50	3	1–5
Hospital stay (Days)	5.06	3.17	4.5	2–23

The mean duration of symptom progression in CBZ and IBZ was 410.3 ± 797.6 and 310.5 ± 774.2 min, respectively. Mean mRS was assessed in both groups at different time periods. Type of CBZ and IBZ infract among BI patients was noted [Table 3]. 28.1% of CBZ and 11% of IBZ patients had bilateral involvement on MRI. The presence of small cortical infracts on MRI and PSCE among BI subjects was evaluated [Table 4].

40% of CBZ and 39.5% of IBZ had no stenosis, 53.3% of CBZ and 53.8% of IBZ patients were in the ICA stenosis group, and 6.7% of CBZ and 7.7% IBZ patients were in MCA stenosis group, with a statistically insignificant relation (p-value >0.05).

12.5% of CBZ and 25% of IBZ patients had critical ICA stenosis. The relation of subjects with the severity of ICA/MCA stenosis [Table 5] and severity of stenosis in relation to the presence of hypotension was assessed. There was no significant difference between the duration of hospital stay among CBZ (median duration—4 days) or IBZ (median duration—5 days) patients.

Discussion

There is a paucity of studies on BI from India. No study from this region evaluated BI. In terms of a single center study, this work is one of the larger attempts (52 BI patients).

Table 3: Type of CBZ and IBZ infract among BI patients

BI infract	Type	N	Percentage
CBZ (N=32)	ACA:MCA BI	2	6.2
	PCA:MCA BI	9	28.1
	BOTH TYPE	21	65.6
IBZ (N=20)	CR	4	20
	CSO	16	80
IBZ (N=20)	Partial	17	85
	Confluent	3	15

Table 4: Presence of small cortical infracts on MRI and PSCE among BI subjects

Small cortical infract	CBZ		IBZ		Total BI	
	N	%	N	%	N	%
Absent	24	75	12	60	36	69.3
Present	8	25	8	40	16	30.7
Total	32	100	20	100	52	100

X^2=1.30; p-value=0.25

PSCE	CBZ		IBZ		Total BI	
	N	%	N	%	N	%
Absent	25	78	18	90	43	82.7
Present	7	22	2	10	9	17.3
Total	32	100	20	100	52	100

X^2=1.21; p-value=0.27

No Indian series was found depicting the prevalence of BI. Our data matched with various studies depicting the prevalence of BI and its subtypes CBZ and IBZ [Table 6].

In the present era, DWI images are essential for the diagnosis and classification of acute ischemic stroke. While different imaging modalities used for classifying BI may be the cause of such variability, the difference in subcategory proportions may also be due to differences in proposed etiopathogenic mechanisms. Also the category of "mixed" both CBZ + IBZ was promoted for the first time in 2017 studies.[12-14] As most radiologists are not familiar with these refinements, it is possible we have missed mixed BI in our study (diagnosis of BI was made on MRI DWI images by radiologist blinded to clinical data).

In the present study, the median duration of symptoms progression was more in CBZ patients (105 min) than in IBZ patients (42 min). Similar to our study, Hiroshi *et al*.[10] mentioned that clinical onset was sudden in 56% and subacute in 44%, manifesting neurological defects over more than several hours. It is uncommon for any vascular etiology to present subacutely, it suggests that HDI in BI may be dynamic. Further controlled studies with larger sample sizes are required to explore this possibility.

In our study, patients with a history of hypotension or hypovolemia were significantly more in the CBZ group; which suggests a role of HDI in CBZ is more than it may be in IBZ. There was no evidence of postural hypotension except in 14.3% of patients of CBZ, which suggests bedside testing of postural fall is not a useful marker of predisposition to BI.

The role of hypotension/hypovolemia among subtypes of BI is debated. The occurrence of CBZ/IBZ only with hypotension/hypovolemia without associated carotid/MCA stenosis has not been studied in detail in any case series. Significant occurrence of symptoms suggestive of hypotension in CBZ in our study is in conjunction with previous studies which showed CBZ result when patients of severe carotid artery stenosis experience a decrease in systemic arterial pressure.

Table 5: Distribution of study subjects in relation to severity of ICA/MCA stenosis

Severity of stenosis	All Subjects						PSCE Excluded					
	CBZ		IBZ		TOTAL		CBZ		IBZ		TOTAL	
	N	%	N	%	N	%	N	%	N	%	N	%
No (0%)	9	28.1	8	40	17	32.7	7	28	6	33.3	13	30.2
Mild (>0–<50%)	4	12.5	1	5	5	9.6	4	16	1	5.7	5	11.6
Moderate (≥50–74%)	12	37.5	6	30	18	34.6	9	32	6	33.3	15	34.8
Severe (≥75%)	7	21.9	5	25	12	23.1	5	24	5	27.7	10	23.4
Total	32	100	20	100	52	100	25	100	18	100	43	100

Chi-square=1.859 with three degrees of freedom; p=0.824 (NS)—(PSCE included) Chi-square=1.08 with three degrees of freedom; p=0.779(NS)- (PSCE excluded)

Table 6: Various studies depicting prevalence of BI and its subtypes CBZ and IBZ

Study	Published Year	Imaging	Total	CBZ	IBZ	Mixed
Bogousslavsky *et al*.[8]	1986	CT head	57	44 (78%)	9 (22%)	None
Weiller C *et al*.[9]	1991	MRI brain T1 and T2	56	36 (64%)	20 (36%)	None
Moriwaki M *et al*.[10]	1997	MRI brain T1 and T2	37	15 (40%)	22 (60%)	None
Yong SW *et al*.[11]	2006	MRI brain- DWI	120	75 (62%)	45 (38%)	None
Li Y *et al*.[12]	2017	MRI brain- DWI	340	92 (27%)	112 (33%)	136 (40%)
El-Gammal TM *et al*.[13]	2017	MRI brain- DWI	66	19 (30%)	26 (40%)	21 (30%)
Weill C *et al*.[14]	2017	DWI	45	13 (28.9%)	1 (2.2%)	31 (68.9%)
Our study	-	MRI brain- DWI	52	32 (62%)	20 (38%)	None

Fluctuating symptoms have been mentioned in BI, but the occurrence of TIA was evaluated only by Yong SW[11] in which 7.5% of patients had prior TIA. We found that hypertension, diabetes, and smoking were more common in IBZ patients as compared to CBZ patients. Similar results and the degree of cerebrovascular stenosis in different types and subtypes of cerebral watershed infarction were observed by Li Y[12] and El-Gammal *et al*.[13]

Results of our study suggested that most BI were not severely disabling infarcts, they tend to improve rapidly, and hospital stay was short. This may in part be due to less cytotoxic edema, small infarct size, and the dynamic nature of watershed circulation. Similar results were observed in the study by Akbur TM *et al*.[15]

Recent literature comparing the prognosis between CBZ and IBZ[11-13,16] has shown higher chances of clinical deterioration and poorer outcomes of IBZ as compared to CBZ. Poor prognosis in IBZ may be deep white matter loss where fibers are densely packed. These results suggested that more intensive care is necessary for patients with IBZ, especially C-IBZ and CR-IBZ.

Cerebral HDI is largely determined by the degree of carotid stenosis.[17,18] Results of several experimental studies (using PET, carotid Doppler, MR perfusion or MRS)[19-24] showed more frequent and severe arterial stenosis in BI patients, increased regional oxygen extraction, and decreased regional cerebral blood flow. Similar to our study, various studies[12-13,25] showed IBZ and especially P-IBZ is more associated with HDI in the brain from large vessel stenosis, while in our study no significant difference was found between ICA/MCA stenosis among CBZ vs IBZ. The reason for that might be a small number of patients in our study as compared to above all studies, but we cannot rule out the possibility of an alternate pathophysiological mechanism.

PSCE, small cortical infarct on MRI outside border zone, and ICA occlusion all can be considered evidence of embolic phenomenon to brain in a patient with BI. We considered moderate to severe ICA occlusion as evidence of HDI. As evidence for embolization to the brain, we compared the presence of small cortical infarct and/or PSCE. The evidence of the embolic origin of BI was reported in four important case series[11-13] which compared CBZ and IBZ directly.

Thus, the result of experimental studies and case series suggest embolism (mainly from stenotic major vessels in the brain) is the main pathophysiological mechanism of CBZ those are not associated with IBZ.

Our study has some limitations. Being a tertiary referral center, there may be a referral bias. Within the time frame of this work, we could not enroll more patients; a larger sample size certainly would have got us a better idea about etiological factors. The vascular imaging modalities were not homogenous (CTA/color Doppler) especially for carotid stenosis.

The presence of small cortical infarcts and PSCE was taken as a marker of embolic stroke. Embolic sources were identified more specifically by high-intensity transient signals using transcranial Doppler ultrasonography. Perfusion images would have been ideal for the exact assessment of cerebral perfusion. Of course, we had to work under logistic constraints; so we chose feasible substitutes for them with scientifically sound bases. Finally, there was no control group in our study.

Further studies are needed to evaluate the effect of early intervention with strategies that increase perfusion pressure, for example, induced hypertension, hypervolemia or emergent revascularization by stenting/endarterectomy in BI patients given its subacute and progressive nature. Studies are also required to know the effects of carotid revascularization on secondary prevention of BI.

Conclusion

Our study found that the association of BI with events causing hypotension or hypovolemia is well-established in our study and warrants caution regarding the imprudent use of antihypertensive drugs. Association of BI with large vessel atherosclerosis is common, and its contribution to CBZ and IBZ seems to be equal. Additional embolic phenomenon appears to be contributing to CBZ. If in the case of BI, no significant stenosis in carotid and/or MCA is found, one must remain alert to the possibility of an embolic source and actively look for it. Traditionally, watershed infarcts are divided into CBZ and IBZ on bases of MRI. At present, many sub-subtypes are increasingly recognized with proposed difference in etiopathogenesis and imaging characteristics. Classification needs revision. Overall prognosis of BI seems to be good, while bilateral multiple BI has very poor prognosis. BI is a

commoner type of ischemic stroke than actually thought of. There is potential for novel approach of treatment, primary and secondary prevention in BI.

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Conflicts of interest

There are no conflicts of interest.

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