Clinical Characteristics of Borderzone Infarction in Egyptian Population

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Objectives: In this research we wanted to highlight the importance of defining Borderzone infarctions (BZI) as a separate subtype in stroke classifications. We thus studied cases of isolated BZI, small vessel disease (SVD), and large vessel disease (LVD), to identify their points of similarities and difference in a sample of Egyptian patients. *Methods:* This is a cross-sectional (observational) study. Consecutive 637 acute ischemic stroke patients were recruited over a 2 year period, from 2 stroke units of Ain Shams University hospitals in Egypt. Medical history and laboratory investigations were done to identify risk factors. National Institute of Health Stroke Scale (NIHSS) was performed on admission, and modified Rankin scale (mRS) on admission, and after 3 months. MRI brain was done to identify stroke subtype; MRA and carotid duplex were used to define vascular status. *Results:* Among the studied group of patients, 72 (11.3%) had BZI, 145 (22.8%) had SVD, 165 (26%) had LVD, and 255 were excluded as they had either undetermined, or mixed etiology. BZI showed significantly older age, early confluent lesions, more disease severity by NIHSS, and worst outcome by mRS ($P < 0.05$). SVD had more microbleeds than BZI and LVD. LVD showed lower prevalence of hypertension and lower high-density lipoprotein levels. *Conclusions:* Isolated BZI, SVD, and LVD infarctions have characteristic risk factors and clinical patterns. Further studies are needed to identify if they are different from cases with mixed pathology. This could have an impact on the selection of primary and secondary preventive measures appropriate to each type.

Key Word: All clinical neurology—all cerebrovascular disease/stroke—borderzone Infarction—small vessel disease—large vessel disease

Introduction

Borderzone infarctions (BZI) have been reported to represent 10%-12.7% of ischemic strokes.[1,2] However, their prevalence might be under estimated as they are not included in the Trial of Org 10172 in Acute Stroke Treatment classification[3] among different stroke subtypes. BZI might be, mistakenly, labeled as large vessel disease (LVD) when MRI shows white matter lesions and greater than 50% intra-cranial or extra-cranial arterial stenosis, or as small vessel disease (SVD) based on MRI picture of deep white matter hyperintense lesions in the absence of vascular stenosis.

BZI might present with transient ischemic attacks (TIAs) and probably those patients do not ask for medical advice.[1]

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The paucity of diagnostic tools as positron emitted tomography (PET) and perfusion studies in acute stroke settings makes the diagnosis of BZI even more unlikely.

Since different stroke subtypes have different pathogenesis, prognosis, and prevention,[1] it is necessary to study risk factors, clinical and radiological presentation, and outcome of each isolated subtype rather than that of mixed pathologies.

However, most of the studies do not state if their stroke population had single or multiple stroke subtypes with predominance of the type being studied.

BZI were defined as "ischemic lesions that occur in characteristic locations at the junction between two main arterial territories."[2] The mechanism of BZI has been ascribed to hemodynamic impairment, but microemboli may also have contribution.[3]

SVD describes white matter hyperintensities, small subcortical infarctions, lacunes, and microbleeds in the absence of significant arterial stenosis.[4] While LVD refers to infarctions larger than 1.5 cm in diameter with arterial stenosis greater than 50%.[1]

Methods

Approval for conducting this study was obtained from Ain Shams University Faculty of Medicine local research ethics committee.

Study Population

A total of 637 Egyptian patients with acute ischemic stroke were recruited over a 2-year period, from 2 stroke units of Ain Shams University hospitals in Egypt. Cerebral infarction was classified into 3 separate clinical categories—BZI,[2] SVD, and LVD, on the basis of the diagnostic criteria of the Trial of Org 10172 in Acute Stroke Treatment study.[5] Those not fulfilling the above or with proven cardioembolic origin were excluded. Only patients with single etiology as determined by the radiological picture were included.

Criteria for subtype allocation:

BZI: are cases with ischemic lesions in watershed areas whether external (cortical) or internal (subcortical), in the presence of extracranial or intracranial atheromatous disease.[2]

SVD: cases showing white matter hyperintense lesions on diffusion and FLAIR, lacunes, or microbleeds, in the absence of intra or extra cranial arterial stenosis or cardiac source of embolization.[5]

LVD: cases with cortical or cerebellar lesions and brain stem or subcortical hemispheric infarcts in the territory of an intracranial artery and greater than 1.5 cm in diameter on MRI, with MRA or carotid duplex showing greater than 50% stenosis or occlusion.[1,5]

In order to study the clinical characteristics of different stroke subtypes, all the patients underwent the following assessment: Medical history and laboratory investigations to identify risk factors: HbA1C, lipid profile, uric acid, echocardiography (to exclude cardioembolism and identify any low cardiac output). National Institute of Health Stroke Scale (NIHSS) was done on admission, and modified Rankin scale (mRS) was done on admission, and after 3 months. MRI brain to identify stroke subtype; MRA and carotid duplex were used to define the vascular status.

White matter lesion burden was estimated according to Fazekas[6] scale and microbleeds were quantified according to Lee et al.[7]

Statistical Analysis

Statistical analysis was done on a personal commuter using IBM SPSS 16th version Statistics (IBM Corp., Armonk, NY). The Kolmogorov-Smirnov goodness of fit test was performed to test the normality of numerical data distribution. Normally distributed numerical data were presented as mean and standard deviation. Qualitative data were presented as number and percentage.

Normally distributed numerical data were compared by the independent-samples (unpaired) Student *t* test to compare the difference in the means between patients. For multiple intergroup comparisons, one-way analysis of variance was used with application of the Scheffé test post hoc whenever a statistically significant difference was detected with one-way analysis of variance.

The Pearson chi square test was used for comparison of groups as regards differences in categorical data. Fisher's exact test was used in place of the chi-square test if greater than 20% of the cells in any cross tabulation had an expected count of smaller than or equal to 5. (All data relevant to the current study have been included in this article, and anonymized data will be shared by request from any qualified investigator.)

Results

Among 637 patients, 145 (22.8%) had SVD, 72 (11.3%) had BZI, 165 (26%) had LVD, and 255 were excluded as they had cardioembolic cause or were of mixed etiology.

The characteristics of study subjects at baseline examination are described in Table 1. The patients with BZI were significantly older than patients in the other 2 groups (P value < 0.01). In LVD the percentage of patients with hypertension was significantly lower ($P = .01$), and those with AF was higher ($P = 0.02$).

The mean values of investigated risk factors are shown also in Table 1. HDL was the only parameter to be statistically different among the stroke subtypes being lower in LVD (37 ± 11.1) compared to SVD and BZI (53 ± 91.6 mg/dL and 40 ± 10.8, respectively) (P value = 0.04; Fig 1).

Table 1. *Demographic data, history of risk factors and results of investigated risk factors*

Stroke subtype Risk factor	SVD (n = 145)	BZI (n = 72)	LVD (165)	*P* value
Age	61.4 (±11.7)	66.6 (±10.5)	58.8 (±11.3)	<.01**
Gender (male sex)	61.4% (89)	61.1% (44)	58.8% (97)	.88
Smoking	42.1% (61)	48.6% (35)	37.6% (62)	.3
Hypertension	71.7% (104)	75% (54)	58.8% (97)	.01**
Rec. CVS	29 % (42)	29.2% (21)	20% (33)	.13
AF	4.1% (6)	4.2% (3)	11.5% (19)	.02*
ISHD	31% (45)	29.2% (21)	28.5% (47)	.88
Uric acid	5.6 (±2)	6.1 (±3.3)	5.6 (±1.8)	.21
HbA1C	7.7 (±2.3)	7.5 (±2.4)	7.5 (±2.2)	.68
LDL	120 (±86.9)	122 (±48.7)	121 (±43.2)	.97
HDL	53 (±91.6)	40 (±10.8)	37 (±11.1)	.04*
cholesterol	184 (±48.9)	191 (±53.5)	189 (±50.3)	.56
TGs	145 (±82.5)	142 (±80.7)	140 (±64.4)	.86
Ejection fraction	61 (±10)	62 (±11)	61 (±12)	.69

Abbreviations: BZI, borderzone infarctions; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVD, large vessel disease; SVD, small vessel disease.
*Statistically significant.
**Highly statistically significant.

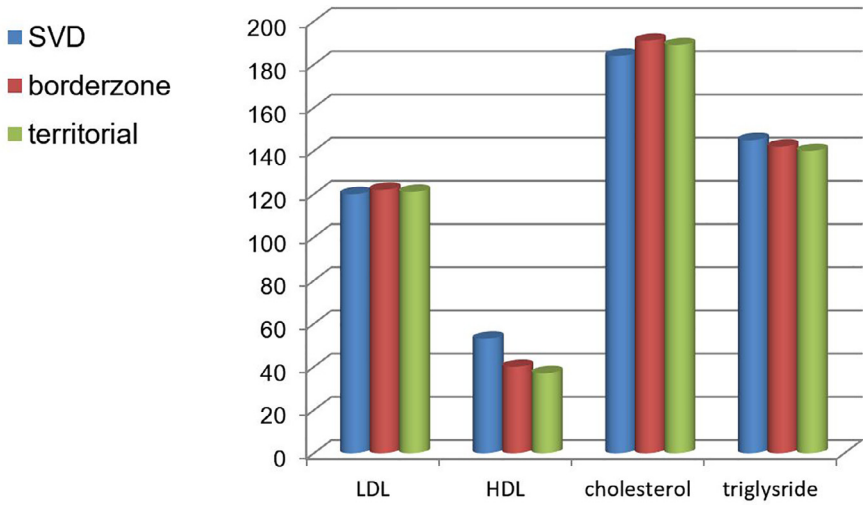

Figure 1. *Lipid profile in different stroke subtypes.*

Clinical severity on admission and clinical outcome are shown in Table 2 and Figure 2. SVD was the least in clinical severity, as assessed by NIHSS, ($P < 0.01$). mRS decreased significantly after 3 months in SVD with higher mean change from admission score, denoting improvement. BZI showed higher scores of mRS on admission yet not reaching significant value while it was significantly higher than the other 2 types after 3 months denoting more residual disability. No significant difference was found between SVD and BZI in lesion burden assessed in FLAIR-MRI by Fazekas scale, though BZI showed more early confluent lesions (Table 3).[6]

Microbleeds were seen in SVD and BZI (58.3% and 34.4%, respectively). However, they were seen in only 7% of cases of LVD (Table 4). Comparing SVD to BZI, microbleeds were significantly higher in SVD ($P = 0.04$; Table 3 and Fig 3).

Discussion

Cerebral infarction is clinically categorized into several subtypes based on the size and pathological changes in the affected arteries.

This study revealed that patients with BZI were significantly older than patients with SVD and LVD. Other authors reported the mean age for BZI to be similar to our patients.[3,4,8,9] However, the mean age for SVD and LVD was higher in other reports in a European population.[10] Although no significant difference was found in gender among the 3 groups, yet male to female ratio was less in LVD 1.5:1 than in SVD and in BZI 2:1.

The prevalence of smoking is variable among different studies[3,4,8-14], reaching as high as 77% for LVD and 50% for SVD[12] and as low as 25% and 18% for LVD and SVD, respectively.[14] Our results showed no significant

Table 2. *Clinical severity and outcome*

Stroke subtype Severity	SVD (n = 145)	BZI (n = 72)	LVD (n = 165)	*P* value
NIHSS	7 (±3)	10 (±4)	9 (±5)	<.01**
mRS admission	3.4 (±0.9)	4 (±1)	3.5 (±1.3)	.06
mRS after 3 months	1 (±0)	3.3 (±2.3)	1.9 (±2.1)	<.01**
mRS mean change (between admission and 3 months)	2.4	1.4	1.9	<.01**

Abbreviations: BZI, Borderzone infarctions; LVD, large vessel disease; SVD, small vessel disease.
**Highly statistically significant.

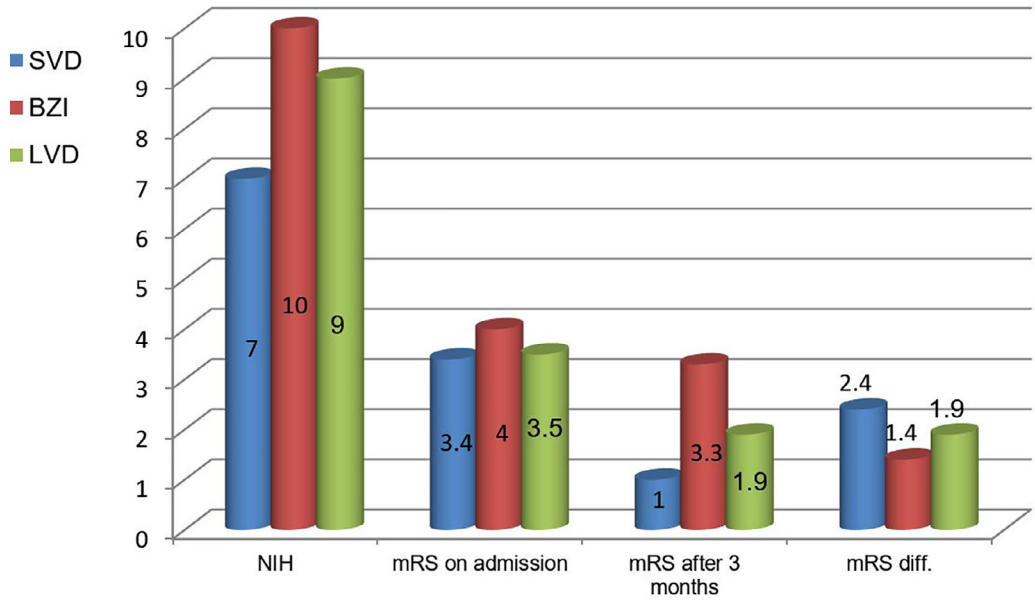

Figure 2. *Clinical severity and outcome after 3 months.*

Table 3. *White matter lesion burden and grading of microbleeds in SVD and BZI*

Stroke subtype		SVD	BZI	*P* value
Fazekas scale	Absent	2.4%	0%	.4
	Punctuate white matter hyperintensities	46.4%	41.4%	
	Early confluent white matter hyperintensities	25%	36.2%	
	Confluent white matter hyperintensities	26.2%	22.4%	
Microbleeds	Absent	41.7%	65.5%	.04*
	Present	58.3%	34.5%	

Abbreviations: BZI, borderzone infarctions; SVD, small vessel disease.
*Statistically significant.

Table 4. *Grading of microbleeds among the 3 groups*

Stroke subtype Microbleeds	SVD	BZI	LVD	*P* value
Absent	41.7%	65.5%	93%	<.01**
Present	58.3%	34.5%	7%	

Abbreviations: BZI, borderzone infarctions; LVD, large vessel disease; SVD, small vessel disease.
**Denotes highly statistically significant.

difference regarding history of smoking between the 3 groups. Smoking was found to be equally prevalent in all types of stroke in several studies.[4,8,9,15]

Hypertension was significantly more prevalent in both SVD and BZI than LVD. It has been previously reported that hypertension is more common in patients with white matter hyperintensities and is correlated with lesion load.[3,4,14,16,17] Some of these studies were conducted on Chinese patients.[3,8,17] Although others reported that hypertension was more prevalent in LVD patients,[10,12] yet Dong et al found no statistically significant difference

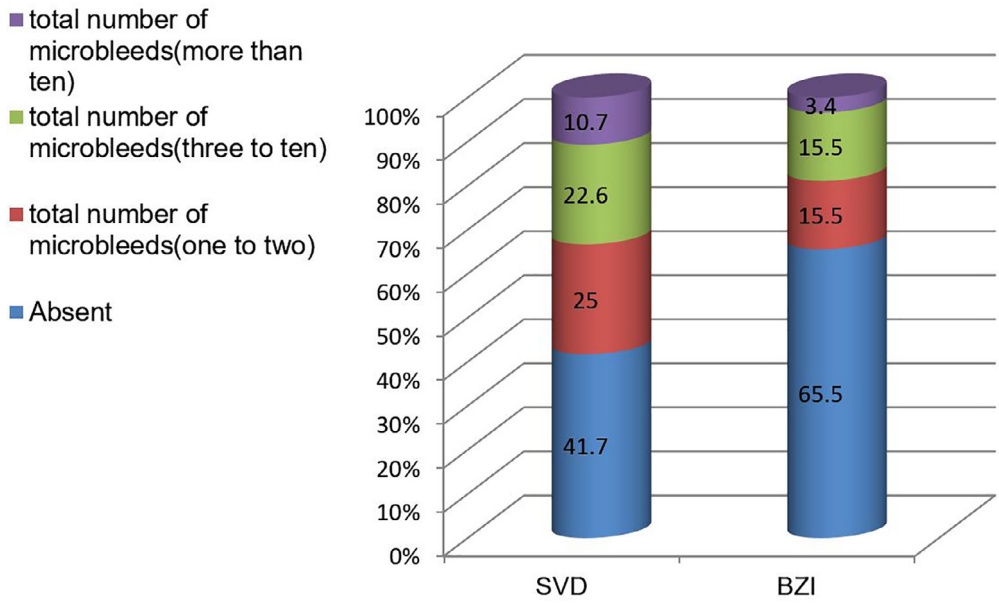

Figure 3. *Grading of microbleeds in SVD and BZI. Abbreviations: BZI, borderzone infarctions; SVD, small vessel disease.*

between BZI and non-BZI patients,[9] and data from several studies showed that hypertension is common in both lacunar and nonlacunar ischemic stroke.[11,18] HbA1C was equally elevated in the 3 groups pointing to the lack of control of diabetes as a risk factor for large as well as SVD. In a systematic review there was marginal excess of hypertension with lacunar versus nonlacunar infarction with no difference for diabetes between both groups.[15]

A history of ischemic heart disease is nearly equal in the 3 groups denoting a systemic vascular risk factor. History of recurrent CVS is quite similar to other studies.[9,11]

HDL was significantly lower both in LVD and BZI than in SVD group, it might not be a major risk factor for SVD in this population, while other lipid assay showed no abnormal findings. Staszewski et al found HDL levels to be lower in lacunar stroke.[19] Hypercholesterolaemia was reported to be present in all types of stroke.[15] In a Chinese population, low-density lipoprotein-cholesterol was more strongly related to LVD than SVD.[20]

Stroke severity assessed by NIHSS on admission lied in the range of moderate stroke, being highest (severer) in BZI and lowest in SVD. Unlike our results, it was reported that BZI showed minor stroke severity.[3,9] The degree of recovery measured by percentage decrease of mRS after 3 months showed least recovery in BZI and best recovery in SVD group. On the contrary, Yong et al found BZI to have better outcome.[9] Similar to our study, several studies showed that severity in SVD is less than that of LVD.[10,20,21] Prera et al found that lacunar stroke had better recovery than other subtypes,[20] and similarly SVD had a better outcome than LVD according to Grau et al.[10]

We compared white matter lesion burden only in SVD and BZI since Fazekas scale is unsuitable for LVD. In spite of the significant difference in severity of presentation, as well as outcome, yet there was no significant difference between SVD and BZI as regards white matter quantification. This might be explained by the difference in underlying pathology. SVD is a manifestation of cerebral arteriolar occlusive disease together with a leaky blood brain barrier.[22] Whereas BZI results from ischemic lesions in an area between 2 neighboring vascular territories, leading to marked neuronal necrosis in these hypoperfused regions.[2,23]

Microbleeds were found in 58.3% of cases with SVD, 34.4% BZI, and 7% LVD. Few studies described the pathological picture of BZI all showing neuronal necrosis but none stating microbleeds.[24,25] On the other hand microbleeds represent a hallmark of SVD.[26,27]

Conclusions

This sample of Egyptian stroke patients with isolated SVD, BZI, and LVD showed that BZI had clinical and radiological characteristic that differ from either LVD or SVD. BZI showed a higher age, severer clinical deficit at presentation and least improvement on follow-up. LVD had less prevalence of hypertension but higher dyslipidemia. SVD presented with least clinical deficit and best outcome of the 3 subtypes. Both BZI and SVD did not differ as regards lesion burden, however, SVD showed significantly more microbleeds. Equally present in all 3 types were smoking, previous stroke, ischemic heart disease, and uncontrolled diabetes.

Recommendations

BZI with its identifying features needs to be considered as a separate entity in clinical and radiological classifications of stroke subtypes.

Also further studies on differences between mixed stroke types and isolated subtypes, their genetic background, pathology, and long term outcome are required.

Appendix A: Authors

Name	Location	Role	Contribution
Nevine El Nahas, MD, PhD	Ain Shams University	Author	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Hossam Shokri, MD, PhD	Ain Shams University	Author	Data collection and analysis including statistical analysis, drafting and revision of manuscript
Osama Abdulghani, MD, PhD	Ain Shams University	Author	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Magd Zakaria, MD, PhD	Ain Shams University	Author	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Taha kamel, MD, PhD	Ain Shams University	Author	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Nagia Fahmi, MD, PhD	Ain Shams University	Author	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Naglaa Khayat, MD, PhD	Ain Shams University	Author	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Aly Shalash, MD, PhD	Ain Shams University	Author	Data analysis, drafting and revision of manuscript
Ahmed El Basiony, MD, PhD	Ain Shams University	Author	Data analysis, drafting and revision of manuscript
Ramez Reda, MD, PhD	Ain Shams University	Author	Data analysis, drafting and revision of manuscript
Sherine Farag, MD, PhD	Ain Shams University	Author	Data collection and analysis, drafting and revision of manuscript
Mohamed Tork, MD, PhD	Ain Shams University	Author	Data analysis, drafting and revision of manuscript
Ahmed Elbokl, MD, PhD	Ain Shams University	Author	Drafting and revision of manuscript
Ihab Abdelbaset, MSc	Ain Shams University	Author	Data collection
Hany Aref, MD, PhD	Ain Shams University	Author	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content

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