BORDER ZONE INFARCTS: A PICTORIAL REVIEW

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ABSTRACT

Border zone or watershed infarcts are ischemic lesions that occur at the junction of two non anastomosing major cerebral arterial territories, constituting approximately 10% of all brain infarcts. Two types of border zone infarcts (BZI) are recognized: Supra tentorial and infra tentorial. Supra tentorial BZI are further of two types; external (cortical) and internal (subcortical). Their pathophysiology has not yet been fully elucidated, but a commonly accepted hypothesis holds that internal BZI are caused mainly by hemodynamic compromise, whereas external BZI are believed to result from embolism but not always with associated hypoperfusion. Various imaging modalities have been used to determine the presence and extent of hemodynamic compromise or misery perfusion in association with BZI. Several advanced techniques (e-g, diffusion and perfusion magnetic resonance imaging and computed tomography, positron emission tomography) can be useful for identifying the pathophysiology, making an early clinical diagnosis and predicting the outcome.

Definition

Border zone infarcts (BZI) also known as watershed infarcts (WSI), are ischemic lesions that occur at the junction of two non anastomosing major cerebral-arterial territories.[1]

BZI were first discussed in the 19th century, Zulch and Behrend reported the typical topographical areas of BZI and hypothesised their haemodynamic mechanism.[2]

These lesions constitute approximately 10% of all brain infarcts.[3]

TYPES:

BZI are classified into two types; Supra tentorial and infra tentorial BZI. We will discuss supra tentorial infarcts in detail.

Supra tentorial BZI are further of two types; external/cortical BZI and internal/subcortical BZI[4] (Fig. 1). External BZI are between two adjacent superficial territories of the anterior (ACA), middle (MCA) and posterior cerebral artery (PCA).[5] These are sub classified as anterior, paramedian and posterior cortical BZI. Anterior cortical border zones and paramedian white matter infarcts are found at the junction of the territories supplied by the ACA and MCA, and those in the posterior cortical border zone

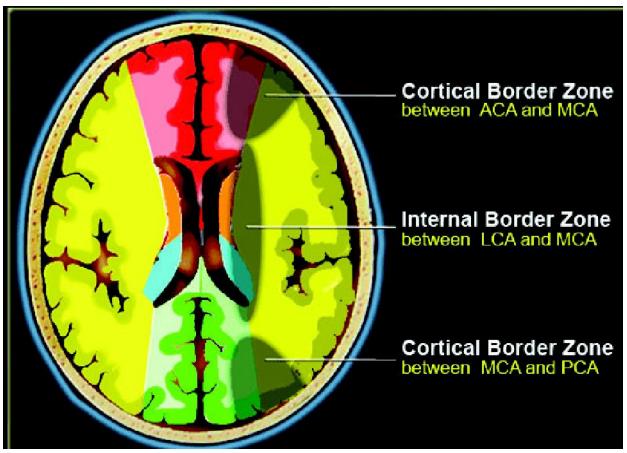

Figure 1

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are found at the junction of the territories supplied by the MCA and PCA. Anterior cortical BZI are more common because of the high prevalence of internal carotid artery (ICA) disease.

Internal BZI are located at the junctions of the ACA, MCA and PCA territories with the Heubner, lenticulostriate (LS), and anterior choroidal artery territories. Internal BZI thus may be classified as infarcts of the LS-MCA, LS-ACA, Heubner - anterior cerebral artery, anterior choroidal - MCA, and anterior choroidal - PCA territories. LS-MCA BZI are the most common as this area is supplied by the end branches of deep perforating LS arteries and medullary penetrators from the pial branches of MCA.[1]

BZI follow the gray and white matter along the length of the parasagittal plane, and show peak infarct frequency at two separate sites. One is frontal peak, in the grey and white matter surrounding the junction of the superior frontal and precentral sulci. And the other is parietal peak, in the grey and white matter of the superior parietal lobule, posterolateral to the post central sulcus.[5] (Fig. 2)

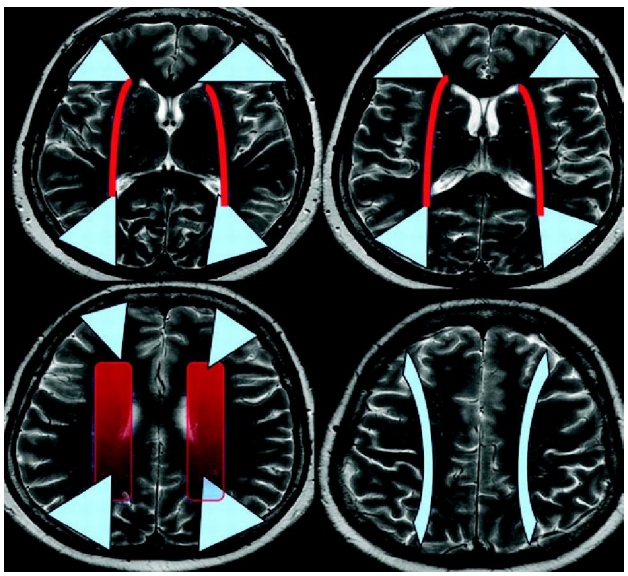

Figure 2: Color overlays on axial T2-weighted magnetic resonance (MR) images of normal cerebrum show locations of external (blue) and internal (red) border zone infarcts.

PATHOPHYSIOLOGY:

Despite much research, the pathogenesis of BZI remains debatable and is thought to be multifactorial. A hemodynamically impaired mechanism including ICA stenosis or occlusion, systemic hypotension, and embolism is a major cause of BZI.[6,7,8] The mechanisms of cortical BZI and internal BZI are presumed to be different.

Cortical BZI are thought to be the result of embolization either from carotid artery atherosclerosis or plaque disruption or from artery-to-artery emboli aggravated by an episode of systemic arterial hypotension. A selective vulnerability of cortical border zone to microemboli is linked to the vascular anatomy of pial arteries supplying those territories, reduced clearance of emboli in a relatively hypoperfused zone, or a combination of both.[9,10]

Internal BZI have been mostly considered to be caused by haemodynamic compromise and severe carotid artery stenotic disease.[11] But there are studies saying that internal BZI result either from hemodynamic impairment or from microembolism secondary to plaque inflammation.[12,13]

The greater vulnerability of internal border zones to hemodynamic compromise is due to anatomic characteristics of the cerebral arterioles within these zones. The medullary penetrating arteries are the most distal branches of ICA and have the lowest perfusion pressure. The deep perforating LS arteries have little collateral supply, and there are no anastomoses between the deep perforators and the white matter medullary arterioles. Therefore, the centrum semiovale and corona radiata are more susceptible than other regions to ischemic insults in the presence of hemodynamic compromise.[1]

MISERY PERFUSION:

Misery perfusion is increased OEF, decreased cerebral blood flow and decreased cerebral blood flow/cerebral blood volume ratio. In symptomatic atherosclerotic cerebral artery disease, misery perfusion is an independent predictor of subsequent stroke risk.[14]

CLINICAL COURSE:

External BZI have a more benign clinical course and a better prognosis because these are closer to the cortical surface thus, increased chance of developing collaterals through leptomeningeal or dural anastomoses.[7] Internal BZI have a poor prognosis and rapid clinical deterioration. Multiple small internal infarcts have proved to be independent predictors of subsequent ischemic stroke.

Patients with metabolic syndrome have greater risk of developing BZI.[15]

INFRATENTORIAL BZI/CEREBELLAR BZI:

Although rare, BZI can also be seen in the posterior fossa between the superior cerebellar artery (SCA) and the posteroinferior cerebellar artery (PICA) or between PICA, SCA and anteroinferior cerebellar artery territories.[16] These are usually less than 2 cm in size, resulting from arterial stenosis or embolism.[1] Isolated vertigo and imbalance may be due to cerebellar BZI, resulting from focal hypoperfusion caused by large artery occlusive disease.[17] Numerous conventional MRI studies unequivocally indicate that migraine with and without aura have an elevated risk of stroke confined to small cerebellar watershed infarcts.[18] (Fig. 3)

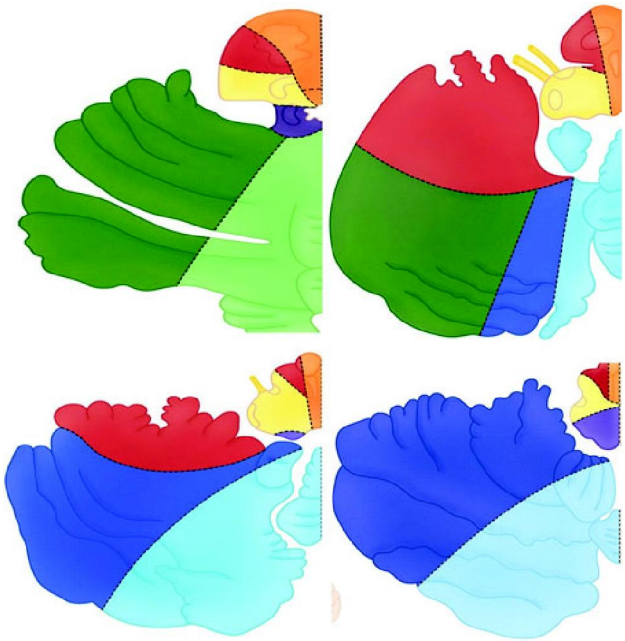

Figure 3: Schematic shows the border zones of the lateral (dark green) and medial (light green) superior cerebellar arteries, anterior inferior cerebellar artery (red), and lateral (dark blue) and medial (light blue) posterior inferior cerebellar arteries. Orange = anteromedial brainstem supply from anterior spinal, vertebral, and basilar arteries; yellow = lateral supply from basilar artery.

IMAGING MODALITITIES:

Transcranial doppler ultrasonography (TCD), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and single photon emission computed tomography (SPECT) are different modalities that provide useful information for identifying the pathophysiologic process, making an early clinical diagnosis, guiding management, and predicting the outcome of BZI.

APPEARANCE:

Internal BZI can appear confluent or partial on CT and MRI. Confluent lesions are due to extensive involvement of white matter and are usually unilateral and runs parallel to the lateral ventricle. Partial internal BZI appear as a single or multiple discrete rounded lesions (rosary bead appearance) in the same distribution as confluent internal BZI.[16,19] (Fig. 4)

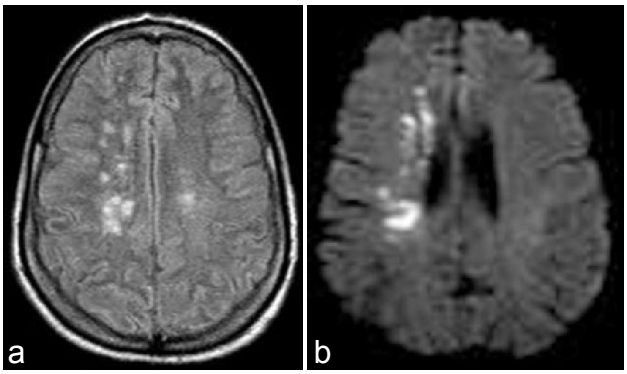

Figure 4: Axial T1 (a) and DWI (b): Multiple right cerebral internal border zone infarcts showing restricted diffusion.

EBZ infarcts appear as fan or wedge-shaped extending from the lateral margins of the lateral ventricle toward the cortex.[16] (Fig. 5, 6)

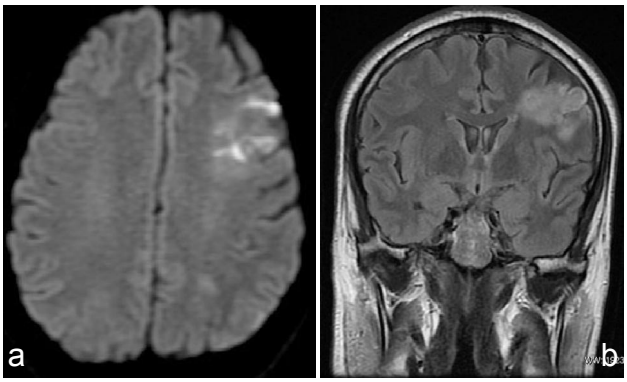

Figure 5: Axial DWI (a) and coronal FLAIR (b): Foci of restricted diffusion in left cerebral hemisphere, predominantly along grey-white matter junction, ACA: MCA territory representing left anterior external watershed infarct.

HAEMODYNAMIC IMPAIRMENT:

Reduction in the cerebral perfusion pressure (CPP) responds by autoregulatory vasodilatation, leading to an increase in cerebral blood volume (CBV), prolongation of mean transit time (MTT) and decreasein cerebral blood flow (CBF). Compromised CBF can be assessed by various techniques, including TCD, stable xenon or ^{133}Xe CT, SPECT, PET, and more

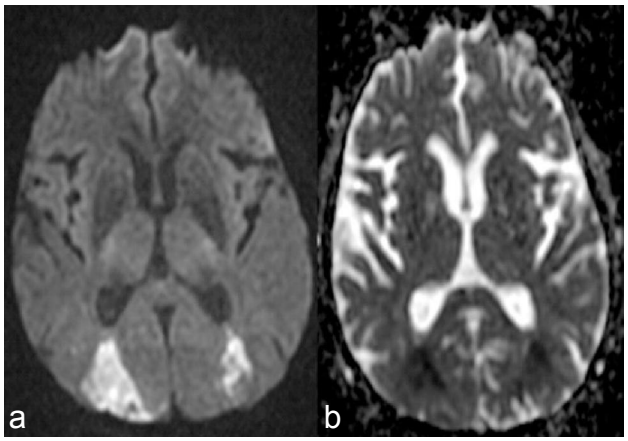

Figure 6: Axial diffusion-weighted MR image and apparent diffusion coefficient map show bilateral posterior cortical border zone infarcts.

recently, CT and MRI perfusion techniques. Most of these are based on evaluation of the autoregulatory response to a vasodilatory stimulus such as intravenous administration of acetazolamide, breath holding or inhalation of carbogen.[16]

Haemodynamic compromise stage 1 is defined as failure of CBF to increase in response to vasodilatory stimulus, because autoregulation has already reached its maximum.[11] A decrease in cerebral blood flow after a vasodilatory challenge represents abnormal response andindicates a higher risk for recurrent stroke.[1]

If cerebral perfusion decreases further, normal cerebral oxygen demand is fulfilled by increasing the amount of oxygen extracted from the blood (OEF) and this is called as haemodynamic compromise stage 2, a phenomenon that can be measured only with PET.

Haemodynamic compromise has been associated with a high risk of recurrent stroke especially for stage 2. The risk of recurrent stroke for patients with an increased OEF is about six to seven times higher than for patients in whom OEF is within the normal range.[11] Elderly patients are more at risk of recurrent strokes in the setting of hemodynamic compromise.[16]

ROLE OF NEUROIMAGING:

The main goals of neuroimaging in patients with BZI is to determine whether hemodynamic impairment is present or not and to assess its severity. Diffusion and perfusion MR or CT imaging are recent advances having increased sensitivity for BZI.

DIFFUSION AND PERFUSION WEIGHTED IMAGING:

Diffusion-weighted MR imaging (DWI) is more sensitive than standard MRI techniques. It can better depict the location of BZI and can differentiate acute stroke from chronic stroke. In acute events, DWI is very sensitive for the diagnosis of both cortical and internal BZI.

Perfusion MR or CT imaging also has been performed in patients with BZI detected at routine CT or MR imaging or DW MR imaging. Perfusion studies help identify misery perfusion associated with BZI and have shown a far greater area of misery perfusion than is reflected on DWI, in patients with internal BZI. Thus, the typically small internal BZI represent the "tip of the iceberg" of decreased perfusion reserve and may be predictive of impending stroke. (Fig. 7) The findings at perfusion imaging could be of greater clinical relevance for identifying acute or chronic stroke. The cause of BZI can also be identified from findings at perfusion imaging.

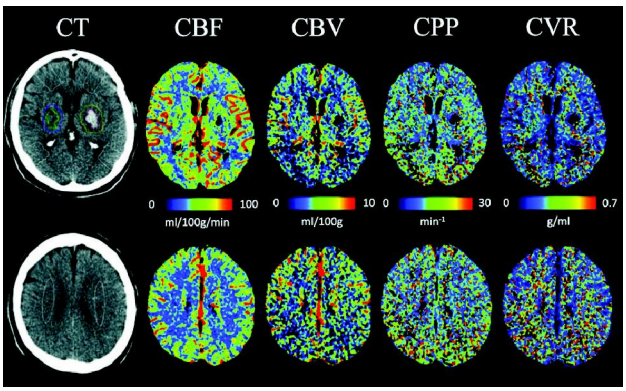

Figure 7: CT perfusion source data with perihematoma and external and internal borderzone ROIs. Maps of cerebral blood flow, cerebral blood volume, cerebral perfusion pressure, and cerebrovascular reserve at 2 different sections from a patient in the <180-mm Hg treatment group.

Three perfusion patterns have been identified; Normal/ transient perfusion deficit, localized perfusion deficit, and extensive perfusion deficit. Recognition of specific perfusion patterns is helps in patient management. Normal perfusion pattern may be seen in patients with a transient perfusion deficit due to decrease in blood pressure, in the absence of any arterial pathology.

Localized perfusion deficit matching the area of restricted diffusion on DWI is often found in patients

with infarcts secondary to embolism. This perfusion pattern predicts relatively good prognosis. (Fig. 8)

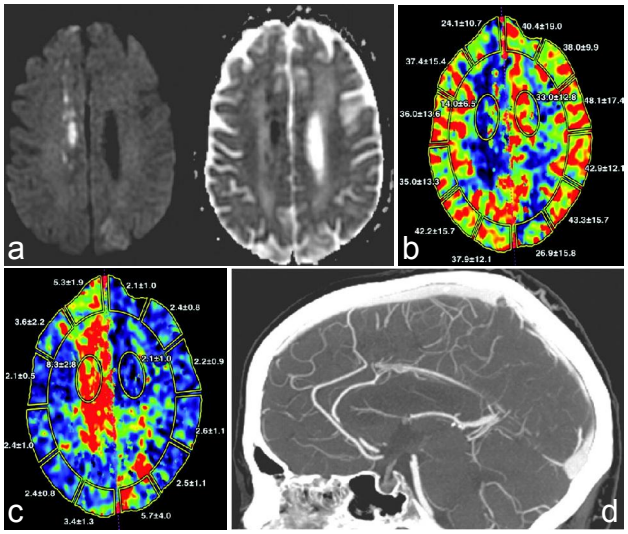

Figure 8: Localized perfusion deficits matching the area of restricted diffusion **(a)** Diffusion-weighted MR image and apparent diffusion coefficient map show regions of restricted diffusion in the territory of the right ACA. **(b, c)** Perfusion CT maps show an area of reduced cerebral blood flow (b) and increased mean transit time **(c)** in the territory of the right ACA **(d)** CT angiogram shows occlusion of an A2 segment of the right ACA.

Extensive perfusion deficits usually involves one or more arterial territories and signaled by a mismatch between diffusion and perfusion imaging findings. It results from severe stenosis or occlusion of large arteries. This perfusion pattern is associated with an increased risk of clinical deterioration and poor prognosis.

PET:

PET evaluation is highly significance in determining the stage II hemodynamic impairment. OEF and CBF are two important parameters that can be measured with PET. Areas with increased OEF and decreased CBF have greater hemodynamic impairment with increased risk of subsequent infarction. (Fig. 9)

SPECT:

Hemodynamic status is evaluated by SPECT using technetium (99mTc)-labeled compounds: 99mTc-hexametazime or 99mTc ethylenecysteine dimer. Cerebral perfusion is measured at baseline and after vasodilatory challenge. Cerebrovascular reactivity measured after vasodilatory challenge has high

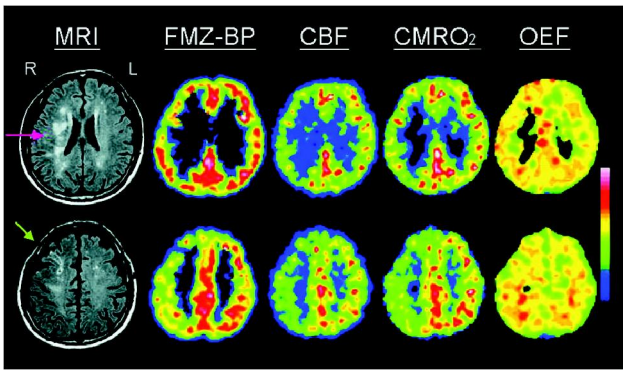

Figure 9: Examples of PET images on 2 different levels show parallel decrease of FMZ-BP, CBF, $CMRO_2$, and an increase of OEF in patient with right ICA occlusion who showed internal border zone infarction (red arrow) with cortical extension (green arrow) on corresponding MR images. In addition to markedly reduced FMZ-BP in region with small cortical infarcts, a decrease of FMZ-BP was found in normal-appearing cerebral cortex beyond border zone infarcts. Mean hemispheric values of ipsilateral/contralateral hemisphere: FMZ-BP ratio, 1.00/1.16; CBF, 20.4/26.1 mL/100 g/min; $CMRO_2$, 2.37/2.87 mL/100 g/min; OEF, 61.9%/58.3%.

sensitivity for the detection of hemodynamically impaired areas. (Fig. 10, 11)

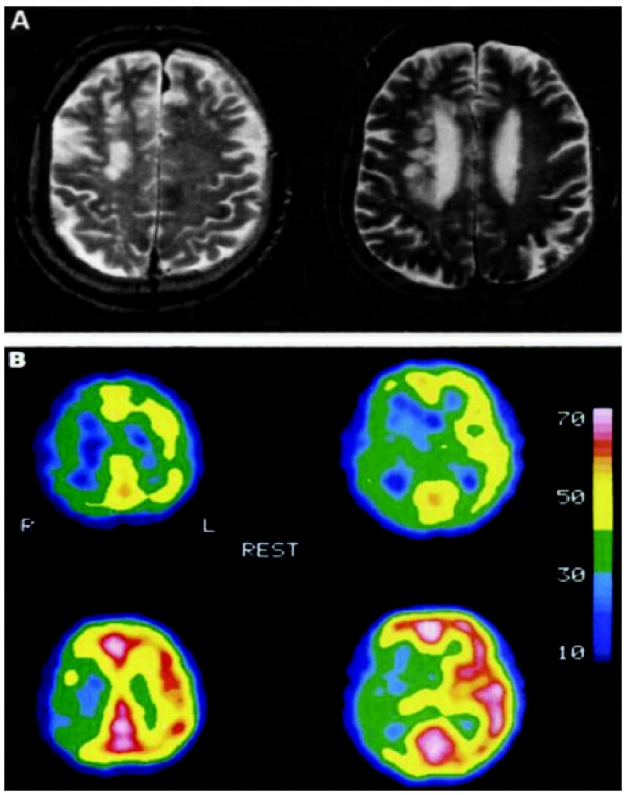

Figure 10: Representative MRI and SPECT images in a patient of deep WS infarct. **(A)** MRI shows deep WS infarcts in the centrum semiovale and corona radiata of the right side, while no involvement of cerebral cortex. **(B)** SPECT images demonstrate low perfusion and de creased acetazolamide reactivity in the right MCA territory.

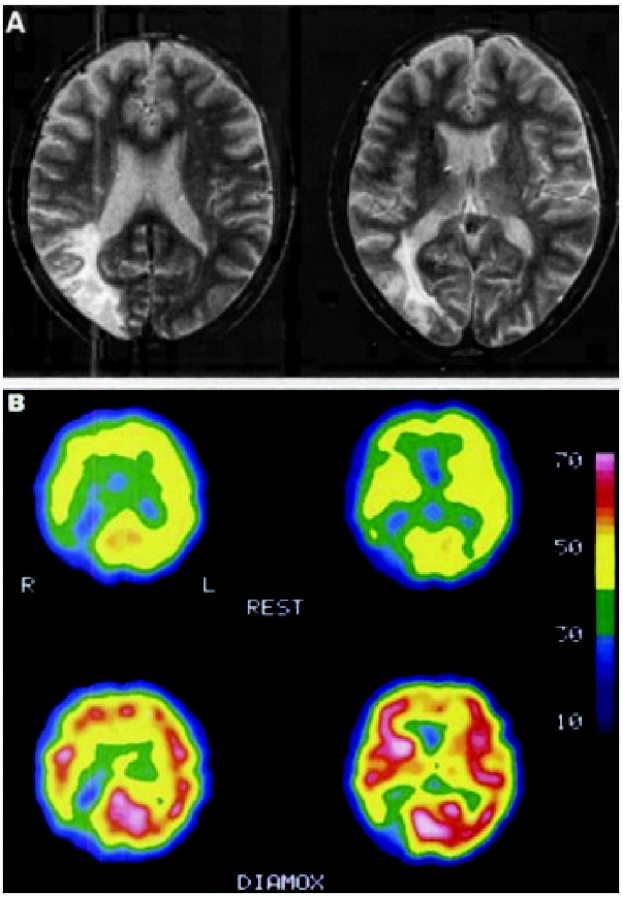

Figure 11: Representative MRI and SPECT imagesin a patient of cortical WS infarct. **(A)** MRI shows cortical WS infarct between the MCA and posterior cerebral artery of the right side. **(B)** SPECT images reveal preserved resting CBF and acetazolamide reactivity, except for the infarcted area.

MRI SPIN LABELLING:

In individual patients, diagnosis of BZI according to the location of the lesion on brain imaging is hampered by the large variability in the territories of the major cerebral arteries. A recent selective arterial spin-labelling MRI study showed that this variability is largely dependent on anatomical variation in the circle of Willis.[20] Perfusion measurements are taken by spin labeling of blood flowing to the individual perfusion territories of major feeding vessels, one vessel at a time. An increase in arterial transit time helpsin the identification of border zones.[1]

Conclusion

Internal/subcortical BZIs typically appear in a linear rosary like pattern, caused mainly by hemodynamic compromise, associated with poor prognosis and higher risk of recurrent stroke. External/cortical BZIs usually follow benign clinical course and are usually caused by embolic phenomenon.

It is essential to differentiate BZI on imaging as different therapeutic approaches may be required for treatment and also to prevent clinical deterioration. Advanced imaging techniques such as diffusion and perfusion MR imaging, PET, perfusion CT and SPECT can be useful for identifying the pathophysiologic process, making an early clinical diagnosis, guiding management, and predicting the outcome.