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Diffusion-weighted magnetic resonance imaging of borderzone necrosis in paediatric tuberculous meningitis

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Abstract

Purpose: Tuberculous meningitis (TBM) is associated with borderzone necrosis (BZN) of the brain parenchyma in areas adjacent to meningeal inflammation. Diffusion-weighted MRI (DWI) allows for accurate detection of cytotoxic oedema associated with necrosis. Detection and characterisation of BZN using DWI to explain its pathogenesis in TBM have not been performed previously in children. Our objective was to identify the prevalence and characteristics of BZN using DWI in children with TBM and to correlate it with the presence, degree and distribution of basal meningeal enhancement (BE) in the absence of large-vessel thrombosis.
Methods: A retrospective descriptive MRI DWI study of 34 children with TBM was conducted. The topography of BZN was compared with the presence and severity of BE on specific MRI sequences.
Results: BZN was identified on MRI DWI in 50% of patients of which 82% had involvement of the temporal lobes. The severity and extent of BE in either middle cerebral artery cistern correlated with the presence of BZN ($P = 0.02$). BZN did not correlate with radiologically detectable vascular occlusion.
Conclusion: BZN is common in TBM occurring in 50% of children. Detection and confirmation of cytotoxic oedema associated with BZN using DWI, and its clear relation to BE supports existing pathogenetic descriptions. The pathogenesis of BZN differs to that of topographical infarction on the basis of distribution as well as an absent statistical relationship between vascular occlusion and BZN.

Key words: cytotoxic brain oedema; diffusion-weighted MRI; encephalitis; meningitis; tuberculous meningitis.

Introduction

Mycobacterium tuberculosis (TB) is a global health concern especially in developing countries where the disease burden is high. As a result of various factors, including the emergence of multidrug-resistant TB strains and the coexisting HIV epidemic, TB meningitis has become the most common cause of bacterial meningitis in the Western Cape of South Africa. Involvement of the central nervous system in TB (CNS TB) predicts a high mortality and serious neurological complications and sequelae. A large percentage of CNS TB occurs in young children and adolescents, with tuberculous meningitis (TBM) being the most common form of CNS TB in this age group.[1]

The concept of borderzone necrosis (BZN) in CNS TB, particularly in TBM, has been alluded to in the literature. Borderzone changes are usually found in advanced disease and indicate a poor prognosis. BZN follows borderzone encephalitis, or inflammation of brain underlying the tuberculous exudate, as a result of extension of exudate along small proliferating vessels into the brain substance, which constitutes a vasculitis leading to ischaemia.[2–8]

BZN has been described in the sylvian fissure, cerebral peduncles, midbrain and pons[2,8–10] but few MRI-based

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studies known to us have been conducted. Furthermore, few studies have specifically included a paediatric population in the characterisation of BZN.

On imaging, T2-weighted sequences are confounding because abnormally high signal in the cortex is not easily distinguished from adjacent cerebrospinal fluid (CSF) or inflammatory exudate.[9,11] It has been suggested that BZN can be detected on fluid-attenuated inversion recovery (FLAIR) imaging,[11] but sensitivity is uncertain. No studies to date have included diffusion-weighted MRI (DWI) to detect the cytotoxic oedema and ischaemic changes associated with BZN. Moreover, BZN has not been correlated with the presence or severity of basal meningeal enhancement (BE) or vascular occlusion as seen on other MRI (contrast-enhanced T1 and T2) sequences to suggest a pathogenetic cause for BZN. BZN has also not been characterised by severity, extent or anatomical localisation.

We hypothesise that BZN in TBM shows cytotoxic oedema (detectable by DWI), and that there is a relationship to the presence, region and degree of localised inflammation in the absence of large-vessel thrombosis.

Materials and methods

This retrospective descriptive study was conducted at a tertiary academic hospital in the Western Cape of South Africa. Ethical approval was obtained by the local health research ethics committee.

Patients younger than 15 years of age with TB meningitis who underwent a brain MRI between August 2006 and January 2008 were considered for the study. From this group, patients diagnosed with TBM on clinical grounds by a paediatric neurologist were selected for the study according to the following criteria:

Proven (CSF culture positive) TBM or, in non-culture-positive cases, characteristic history and CSF chemistry changes in addition to a minimum of three further criteria (weight crossing centiles, Mantoux positivity, compatible chest X-ray, TB contact, CT or MRI features of TBM, non-cerebrospinal bacteriological confirmation, and response to appropriate drug therapy).

Patients with inadequate imaging, for example, those who have an unavailable DWI or contrast examination, were excluded from the study.

Magnetic resonance imaging (MRI) at 1.5 T was performed using a standardised protocol. A T2 turbo spin echo sequence was used in the axial and sagittal planes. A FLAIR sequence and a T1 turbo spin echo sequence before and after contrast administration were used in the axial plane. An echo planar DWI sequence in the axial plane was included repetition and echo times of 6500/125 ms; field of view, 24×24 cm; matrix, 128×128; slice thickness, 5 mm with 2.5-mm gaps; two *b*-values of 0 and 1000 s/mm^2) and apparent diffusion coefficient (ADC) maps calculated (Magnetom Symphony 1.5 Tesla, Siemens AG, Erlangen, Germany; 0.1 mmol/kg IV Magnevist®, Bayer Schering Pharme AG, Leverkusen, Germany).

The MRI scans were reviewed retrospectively by a consultant paediatric radiologist with extensive TBM imaging experience. The presence or absence and anatomical localisation of BZN on DWI, the presence, location and grading of BE on a gadolinium-enhanced T1-weighted sequence, and the presence of vascular occlusion as per loss of flow void on T2-weighted sequence were all recorded.

Regions inspected for BZN included areas of the brain adjacent to the cisterna lamina terminalis, the left and right frontal- and temporal-sided middle cerebral artery (MCA) cisterns, the left and right sylvian fissure[,] and the left and right temporo-occipital- and cerebellar-brainstem-sided ambient cisterns, yielding a total of 12 areas per patient. The areas were also combined to designate clinically relevant regional BZN frequencies: temporal and frontal lobes, and brainstem involvement on either side of and adjacent to cisternal areas of possible inflammatory exudate.

An area was considered positive for BZN if it appeared hyperintense on DWI while hypointense on the corresponding ADC map in at least two contiguous axial images.

BE on gadolinium-enhanced T1-weighted imaging was graded as *mild to moderate* when the 'double-line sign' was demonstrated, indicating enhancement-abutting lobes or separated by vascular flow void.[5] A *severe* grading for BE was given when the normal cisternal appearance was obliterated or 'filled' by a thick and nodular enhancement pattern.

Loss of arterial flow void was recorded on T2.

Locations of BZN were subsequently matched with corresponding anatomical locations of BE, BE severity grading and presence of vascular occlusion, and then statistically correlated using maximum likelihood chi-squared categorical data analysis. In all analyses, a significance level of $P = 0.05$ was used.

Results

Thirty-four patients were selected for the study on the basis of our diagnostic criteria. Thirteen were male and 21 female, with a mean age of 4.4 years, a median of 3.5 years and an age range of 0.3–14.8 years.

BZN was identified in 17 (50%) of the study group. Fourteen of these patients (82%) had temporal lobe involvement, six (35%) had frontal and three (17%) had brainstem involvement. Right- and left-sided disease occurred with equal frequency and bilateral disease occurred in seven (41%) (Fig. 1), predominantly in the temporal lobe. The distribution of BZN is summarised in Table 1.

BE was most prevalent in the MCA cisterns with 28 patients (82%) having either left- or right-sided

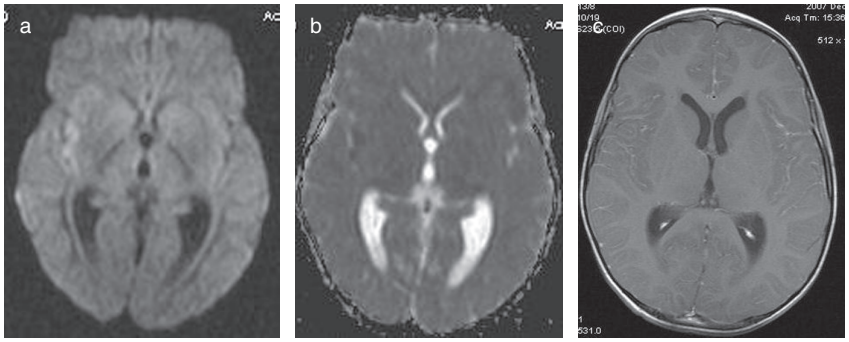

Fig. 1. Borderzone necrosis in a 4-year old involving the perisylvian cortex. (a) DWI demonstrates bilateral sylvian increased signal predominantly involving the insula. (b) ADC – subtle restricted diffusion at the right insula and left frontal operculum. (c) There is mild abnormal meningeal enhancement on the left adjacent to the frontal operculum. ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging.

involvement (Figs. 2c,3c). Twenty-six patients (76%) had ambient cisternal enhancement, 19 (56%) had involvement of the cisterna lamina terminalis and 19 (56%) showed perisylvian contrast enhancement. *Mild to moderate* BE was more prevalent than *severe* BE (55% vs 8.4%) (Fig. 4c) and was most prevalent in the MCA (76%) and ambient cisterns (71%). See Table 2 for these relationships.

Table 1. Distribution of BZN instances by lobe in patients positive for BZN

Region of brain	Subregion	Total/Right/Left	Number of instances (204)	Number of patients
Temporal		Total	23 (11.3%)	14 (82%)
	Posterior to MCA cistern	Total	18	
		Right	9	
		Left	9	
	Adjacent to ambient cistern	Total	0	
		Right	0	
		Left	0	
	Perisylvian	Total	5	
		Right	3	
		Left	2	
Frontal		Total	9 (4.4%)	6 (35%)
	Adjacent to ACA cistern	Total	4	
		Right	2	
		Left	2	
	Anterior to MCA cistern	Total	5	
		Right	2	
		Left	3	
Brainstem		Total	4 (1.7%)	3 (18%)
		Right	2	
		Left	2	

BZN, borderzone necrosis; MCA, middle cerebral artery; ACA, anterior cerebral artery.

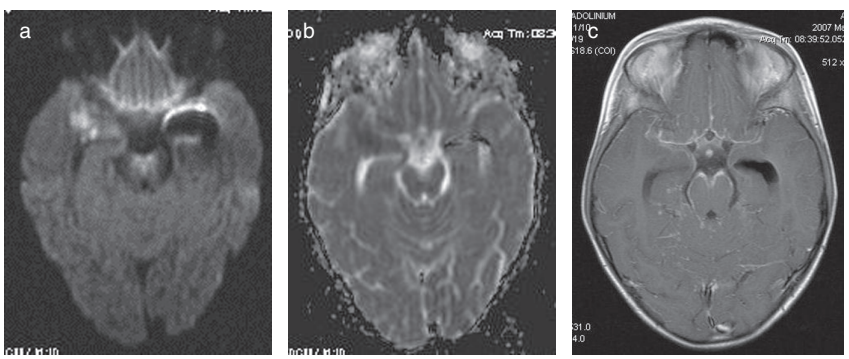

Fig. 2. Borderzone necrosis on either side of the right MCA cistern in a 7-year old with TBM. (a) DWI demonstrates increased signal abnormality in the temporal lobe and frontal lobe on either side of the right MCA cistern (on the left the cistern is obscured by artefact because of air in the ventricle). (b) ADC shows reduced signal confirming the restricted diffusion. (c) Gadolinium-enhanced T1-weighted MRI demonstrates bilateral mild enhancement of both MCA cisterns as well as enhancement of the optic chiasm. ADC, apparent diffusion coefficient; DWI, diffusion-weighted MRI; MCA, middle cerebral artery.

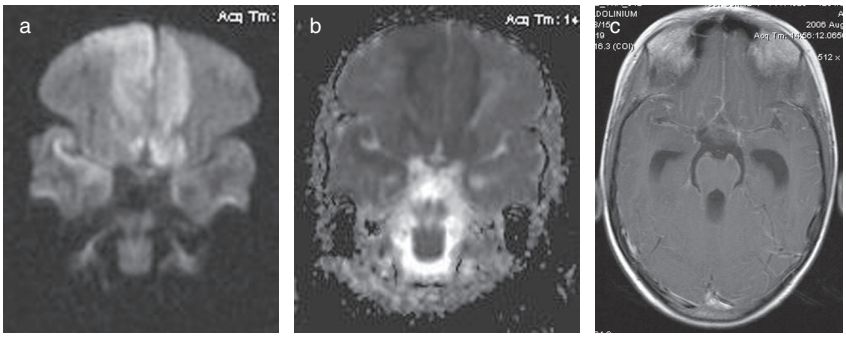

Fig. 3. Borderzone necrosis of the right MCA cistern in a 9-year old with TBM. (a) In addition to topographic bilateral ACA infarcts, there is also assymetrically increased signal in the parenchyma on either side of the right MCA cistern consistent with BZN. (b) ADC confirms restricted diffusion related to the ACA infarct and the right zone bordering the MCA cistern. (c) Very subtle bilateral basal meningeal enhancement is present lining the frontal and temporal lobes on either side of the MCA cisterns. ACA, anterior cerebral artery; ADC, apparent diffusion coefficient; BZN, borderzone necrosis; MCA, middle cerebral artery.

Vascular occlusion was demonstrated in a minority of patients, with the highest frequency in the MCAs (9%) (see Table 3). Vascular mottling (Fig. 5a) seen in relation to the MCAs occurred in 10 patients (29%).

Two patients were noted to have topographic MCA infarcts (Fig. 5) and one had an anterior cerebral artery territory infarct (Fig. 3).

A statistically significant relationship was demonstrated between BZN and BE distribution in the regions adjacent to either MCA cistern ($P = 0.02$). BZN was independent of the severity of its corresponding BE. Positive correlation ($P = 0.04$) was demonstrated between the presence of BZN adjacent to the right MCA cistern and a mottled appearance to the MCA on the same side. The presence of vascular occlusion was statistically unrelated to both BZN and BE.

Discussion

Involvement of the CNS TB predicts a high mortality rate and potentially serious neurological complications and sequelae.[1] CNS TB occurs in all age groups, but 60–70% occurs in the sub-20-year age group.[12] Of all tuberculous cases, 2–5% affect the CNS[13] and the CNS is affected in 10% of AIDS-related TB cases.[14] TBM is the most common and most lethal presentation of CNS TB and occurs mainly in young children and adolescents.[1]

In this diffuse type of granulomatous inflammation, the basic pathology is characterised by a thick, predominantly basal, exudative leptomeningitis. Numerous important complications exist including hydrocephalus, nerve palsies, infarction, encephalitis and BZN.[1,2,4,15]

Cerebral infarction, arising from a progressive basal inflammatory exudate involving the vascular wall leading to a panarteritis, thrombosis and vascular occlusion, occurs predominantly in the basal ganglia and internal capsule from occlusion of basal perforators (especially the lenticulostriate arteries). Magnetic resonance imaging (MRI) is generally considered superior to CT for demonstrating basal ganglia infarction, appearing as T2 hyperintensities with or without gadolinium enhancement.[1]

Borderzone encephalitis refers to inflammation in brain tissue immediately underlying the tuberculous exudate, resulting from extension of the exudate along small proliferating blood vessels into the brain substance, which in turn constitutes a vasculitis leading to focal and diffuse ischaemia.[6,16] When infarcts occur adjacent to *severe* meningeal and cisternal inflammation, the areas are considered 'border-zone' infarction.[5] We refer to this as BZN, as this term more accurately describes the theories underlying the pathology, which consists of gliosis, oedema (including cytotoxic) and perivascular infiltration involving epitheloid cells. These cells, together with others like lymphocytes and plasma cells, infiltrate the walls of small blood vessels, causing

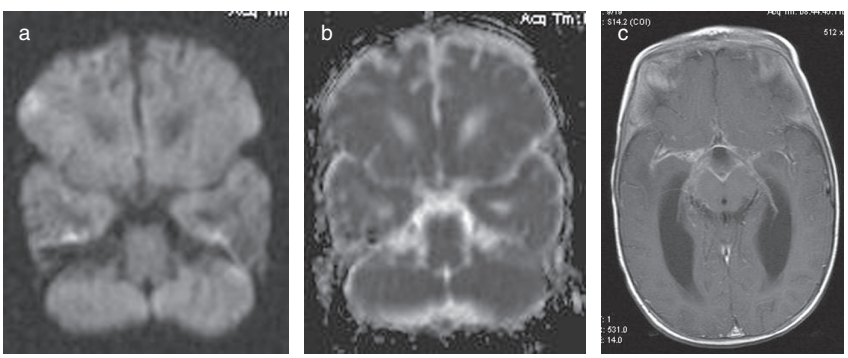

Fig. 4. Bilateral temporal borderzone necrosis associated with *severe* right and *mild to moderate* left basal meningeal enhancement. (a) DWI demonstrates subtle increased signal involving the temporal cortex adjacent to the MCA cistern bilaterally. (b) ADC mapping confirms restricted diffusion at both sites. (c) Gadolinium enhanced T1 MRI demonstrates *severe* enhancement in the right MCA cistern and *mild to moderate* enhancement lining the left MCA cistern. ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; MCA, middle cerebral artery.

Table 2. Instances of basal meningeal enhancement by location, graded by severity

Location of basal meningeal enhancement	Mild to moderate (238)	Severe (238)
Rt MCA cistern	24 (10.0%)	3 (1.3%)
Lt MCA cistern	23 (9.7%)	4 (1.7%)
Cisterna lamina	17 (7.1%)	2 (0.8%)
Rt ambient cistern	24 (10.0%)	3 (1.3%)
Lt ambient cistern	20 (8.4%)	3 (1.3%)
Rt perisylvian region	14 (5.9%)	3 (1.3%)
Lt perisylvian region	10 (4.2%)	1 (0.4%)
Total instances	132 (55.5%)	20 (8.4%)

MCA, middle cerebral artery; Rt, right; Lt, left.

vasculitis and necrosis in neural tissues related to both the intracranial (mainly basal) and spinal leptomeningeal exudate.[16]

Integral to BZN is cytotoxic oedema, affecting predominantly grey matter, which is thought to reflect increased intracellular water following adenosine triphosphate depletion because of ischaemia, whereas vasogenic oedema indicates an increase of extracellular water from rising transvascular pressure often associated with heightened vascular permeability. Ischaemic brain oedema is initially cytotoxic because of disturbances in cell membrane integrity. Later, vasogenic oedema sets in because of disruption of the blood-brain barrier.[17]

Magnetic resonance imaging (MRI) for BZN includes T2, FLAIR and DWI with ADC mapping. BZN alone is very difficult to see on T2, as both it and the characteristic leptomeningeal exudate appear bright,[9,11] and also because normal cisternal CSF is bright on T2. It has been suggested that BZN can be seen on FLAIR, along with perivascular demyelination, as a hyperintense area.[11] This, however, is not a specific finding of necrosis and may indicate vasogenic oedema.

DWI, used in our study population, allows for the suppression of diffusion signal from normal background brain tissue and CSF allowing for better lesion contrast.[18] DWI in combination with ADC maps can reveal cytotoxic oedema associated with BZN. DWI has advantages over FLAIR and T2-weighted MRI as it is more sensitive for detecting acute and subacute infarctions, as well as depicting the involved area more accurately in patients with TBM.[19] This is most probably true for other causes of cytotoxic oedema including BZN. A potential disadvan-

Table 3. Instances of borderzone necrosis, basal meningeal enhancement and vascular occlusion by standardised location

Grouped locations for purposes of correlation	Borderzone necrosis (238)	Basal meningeal enhancement (238)	Vascular occlusion (238)
R MCA/cistern	9 (3.8%)	27 (11.3%)	3 (1.3%)
L MCA/cistern	9 (3.8%)	27 (11.3%)	3 (1.3%)
ACA/cisterna lamina terminalis	2 (0.8%)	19 (8.0%)	1 (0.4%)
R PCA/ambient cistern	2 (0.8%)	26 (10.9%)	0 (0%)
L PCA/ambient cistern	2 (0.8%)	23 (9.7%)	1 (0.4%)
R sylvian branches of MCA/perisylvian region	3 (1.3%)	17 (7.1%)	2 (0.8%)
L sylvian branches of MCA/perisylvian region	2 (0.8%)	11 (4.6%)	2 (0.8%)
Total instances	29 (12%)	150 (63%)	12 (5%)

ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.

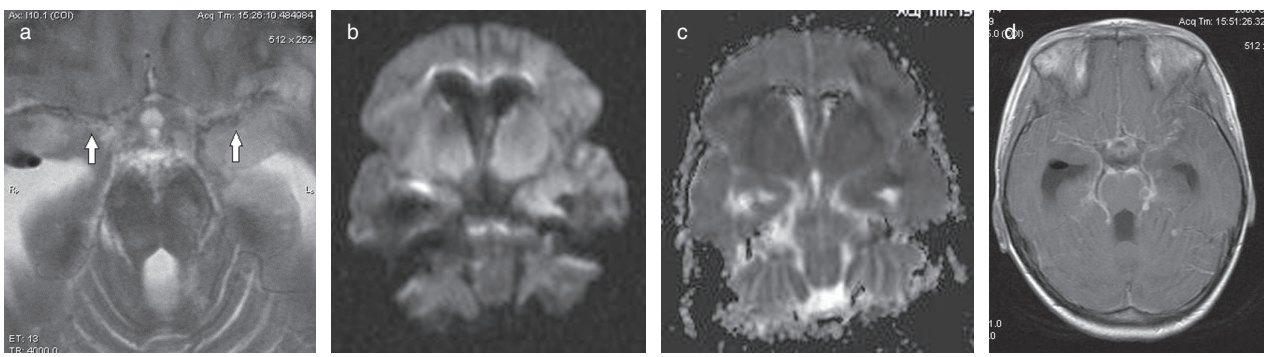

Fig. 5. T2 mottling associated with borderzone necrosis at both MCA cisterns. (a) T2-weighted MRI demonstrates a mottled pattern to the MCA vessels possibly related to vasculitis (white arrows). (b) DWI shows increased signal involving the temporal lobes bilaterally corresponding to borderzone necrosis but anterior to the MCA cistern this is difficult to separate out because of a topographic infarct. (c) ADC mapping confirms restricted diffusion at both sites. (d) Gadolinium-enhanced T1 MRI demonstrates moderate basal meningeal enhancement bilaterally at the MCA cisterns. ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; MCA, middle cerebral artery.

tage of DWI is that because of its time dependence, chronic infarctions may only be visible on T2 or FLAIR. The timing of imaging relative to neurological symptom onset was not recorded, nor was follow-up imaging, and might have been valuable to demonstrate potentially reversible cytotoxic oedema. These shortcomings may form the basis for further study.

B-values of 1000 were used in our study because of its increased sensitivity for cytotoxic oedema by reducing the T2 effect. Increasing the *b*-value may further improve sensitivity to water motion, and although runs the risk of motion artefact, has been shown to increase lesion conspicuity in children.[20]

There is a definite paucity in the literature concerning BZN that has either measured an incidence or related it to BE in order to postulate a link between the two. BZN has also not been characterised by type and anatomical location or related to distribution of large-vessel occlusion. DWI has never before been used to demonstrate its presence by detecting cytotoxic oedema.

The regional-measured prevalence of BZN in our study did not correspond with existing measured data. A propensity for the area posterior to the MCA cistern in the temporal lobe (affecting the amygdala and caudate tail), in our study, seemed to contrast with a previously described preference for the sylvian fissures, described in studies of post-mortem specimens.[2,21] Other descriptions of regional frequency were difficult to compare because of differences in localisation criteria, for example, the cerebral peduncles abutting the interpeduncular fossa, as well as the midbrain and pons adjacent to areas of cisternal enhancement.[8–10] The latter studies also employed CT and MRI without DWI, which have not shown adequate specificity in demonstrating BZN.

The high percentage of temporal lobe involvement demonstrated is clinically relevant as important functions, such as speech and visual processing, as well as memory may all potentially be affected.

Our correlative results lend some support to the existing pathogenetic descriptions of borderzone disease. A clear relationship between left or right MCA BZN, and corresponding MCA cisternal enhancement was encouraging as this supports existing descriptions of it occurring in areas of the brain subtending severe cisternal inflammation. Importantly, BZN was also never seen without BE in our patients, further emphasising the aforementioned pathogenesis. Little other significant correlation was seen in other (BZN/BE) distributions, including the ambient cisterns, cisterna lamina terminalis and sylvian fissures. This may be a reflection of the small study population employed and larger sample populations would be desirable to confirm these findings.

Severity of intrapatient BE by region did not correlate with the presence of BZN when corrected for laterality. This implies that BZN, although clearly linked to BE, appears not to depend on its severity. Previous work detailing BE severity on CT revealed no correlation with clinical stage,[22] and it remains to be seen whether the presence of BZN correlates with clinical disease severity.

Positive correlation between MCA *mottling* and BZN adjacent to the MCA cistern may be significant. We postulate that mottling represents a diseased MCA either in the form of non-occlusive vessel wall granulomas or a vasculitis. In one study that included gross pathology, granulomas here were said to be rare but occasionally present.[2] Fisher demonstrated that non-occlusive parent artery disease often mediates perforating artery infarcts, although that study related to basal artery atherosclerosis.[23] TBM has been associated with large-vessel vasculitis, though.[15] Larger arteries, such as the MCAs, have been shown to demonstrate periarteritis, which may explain the mottled appearance to the MCA seen in our study. The specific relation to BZN may then be due to an extension of this process yielding a necrotising panarteritis with secondary thrombotic occlusion in the smaller branching MCA vessels.[24]

No correlation was shown between the intrapatient presence of BZN and large-vessel occlusive disease. This may support the proposed underlying mechanisms; if BZN (gliosis) follows perivascular inflammation and cytotoxic oedema because of spread of basal exudate along the adventitia, we postulate that vascular occlusion resulting in topographic cerebral infarction has a different pathogenesis, such as exudative strangulation of vessels with or without dilated ventricles stretching already compromised vessels.[2,25]

Borderzone disease has been said to predict a poor outcome.[8] One study[26] using DWI and ADC mapping to examine cytotoxic oedema showed that presence of the latter can herald cerebral infarction. Its vasogenic counterpart was shown to be relatively reversible. A similar study[27] suggested a poorer outcome in cases of cytotoxic oedema seen on DWI in the setting of acute disseminated encephalomyelitis. It can therefore be argued that, if available, inspecting the DWI and ADC mapping in TBM for cytotoxic oedema, particularly in the MCA regions, may be of value in prognostication. Some areas showing restricted diffusion may revert to normal over time, but without the use of perfusion imaging (not widely available in developing countries) or follow-up studies, prognostication using DWI alone may be inaccurate. MCA mottling on T2 may predict the coexistence of BZN, which may help as a surrogate marker thereof in the absence of DWI and ADC mapping.

Study limitations include its retrospective nature and lack of radiological–clinical–pathological correlation. Radiological–clinical correlation in TBM is complicated by the fact that TBM is a diffuse vasculitic disease resulting in multiple rather than localised deficits, and may sometimes even be progressive on treatment. Radiological–pathological correlation is difficult as post-mortems in children with TBM are often difficult to obtain owing to parental resistance.

Conclusion

BZN has a significant prevalence in children with TBM and is important because it is reported to predict a poor prognosis. This is especially true as it seems to show a propensity for the temporal lobes, helping us understand the often poor-resulting neurological outcome.

We have shown a significant relationship between the presence of BZN on DWI and BE, supporting existing descriptions of it occurring in areas of the brain subtending severe cisternal inflammation. The relationship, however, was only statistically significant in the MCA territory and differed to other studies describing other more prevalent regions. This may be a result of our small study population, or because we have used more sensitive imaging, and more studies are needed to further investigate this aspect.

Mottling of the MCA on T2, whether representing a vasculitis or other non-occlusive vessel disease, may predict the presence of BZN on DWI and may act as a surrogate marker of BZN in the absence of DWI and ADC mapping.

Our findings suggest that BZN should be sought for and reported using DWI MRI when imaging children with TBM, particularly surrounding the MCA regions, and that the appearance of mottling of the MCAs may similarly be used to predict BZN. We suggest further research with larger patient groups comparing these radiological findings with patient outcome.

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