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Magnetic Resonance Imaging Evaluation of Suspected High-Altitude Cerebral Edema in Patients from High Altitude

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ABSTRACT

Background: Trekkers in high altitude of Himalayas could lead to Acute Mountain Sickness and High Altitude Cerebral Edema. This study was conducted to evaluate magnetic resonance imaging findings among the clinically suspected High Altitude Cerebral Edema patients rescued from high altitudes in Nepal Himalayas.

Methods: 49 patients with clinically suspected High Altitude Cerebral Edema were retrospectively evaluated in this cross-sectional study who were sent for a brain magnetic resonance imaging. They were categorized in 3 groups according to the magnetic resonance imaging features in this study.

Results: There was a slight male preponderance. 6 patients (12.25%) had magnetic resonance imaging findings highly suggestive of High Altitude Cerebral Edema. 5 patients had T2 high signal intensity and restricted diffusion in the splenium of corpus callosum of which 3 had features of microhemorrhage. One patient with normal brain morphology and intensity in T1, T2, and FLAIR images showed innumerable variable-sized microhemorrhages in Susceptibility Weighted Imaging. 14 of patients showed various T2 and FLAIR white matter high signal intensity without restricted diffusion. And one patient had features of subacute lacunar infarcts. 28 patients (57.14 %) showed no abnormal signal changes in the magnetic resonance imaging scan.

Conclusions: Typical magnetic resonance imaging features of cytotoxic edema in corpus callosum and microhemorrhage in the patients with High Altitude Cerebral Edema further support the findings in other similar studies. T2 white matter hyperintensities in deep, subcortical or periventricular location and lacunar infarcts could be seen in High Altitude Cerebral Edema. Normal magnetic resonance imaging of the brain is not infrequent.

Keywords: Acute mountain sickness; high altitude cerebral edema; magnetic resonance imaging; microhemorrhage; susceptibility weighted imaging

INTRODUCTION

Each year tens of thousands of people travel to the Himalaya ranges of Nepal and are exposed to hypobaric hypoxia.[1] This could lead to acute mountain sickness (AMS) and High Altitude Cerebral Edema (HACE). True incidence of progression from AMS to HACE is difficult to assess by clinical features only. Magnetic resonance imaging (MRI) delineates changes along with the extent of the disease in the brain. The most common MRI brain findings in HACE are increased T2 and FLAIR signal in the splenium of the corpus callosum with restricted diffusion, T2 white matter hyperintensities and microhemorrhages.[2-3]Many studies were conducted in AMS and HACE taking clinical findings in trekkers and pilgrims in Nepal.[4-7] However, no study in Nepal has been published with the evaluation of MRI findings to date. Therefore, this study was conducted to evaluate MRI findings among the clinically suspected HACE patients rescued from high altitudes in Nepal Himalayas.

METHODS

This was a retrospective, cross-sectional observational study. High altitude illness comprises spectrum of clinical conditions such as AMS, HACE, High Altitude Pulmonary Edema (HAPE). There is scoring system for AMS by Lake Louise AMS score which consider severity

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of headache, gastrointestinal symptoms, fatigue and/or weakness and dizziness/light-headedness (score of each ranges from 0-3). It suggests mild form with 3-5 points, moderate 6-9 points and severe 10-12 points.[8] There is modification on it also, considering headache as a hallmark of AMS. Progression from AMS to HACE is followed by signs of encephalopathy with ataxia and altered mental status from confusion, behavioural changes to unconsciousness mild to severe AMS and HACE are clinical diagnosis and there is overlap in signs and symptoms between moderate to severe AMS and HACE. HACE comprises of sign and symptoms of ataxia and altered mental status with or without AMS. The altered mental status may range from mild to severe with symptoms of severe headache lassitude and decline in level of consciousness and focal neurological deficits or seizures. Patients with clinically suspicion of HACE with a history of air evacuation from high altitudes patients were included in this study who were sent for brain MRI from local hospitals of Kathmandu. Therefore, a convenient sampling technique was used. MRI of all these patients with HACE from 2014 through 2019 were evaluated. Ethical approval was obtained from the Institutional Review Committee (IRC) of the Nepal Health Research Council (NHRC). Consent was taken from each patient. MRI was done in 3 Tesla (3T) Philips Ingenia platform, at Jeebanta Advanced Kathmandu Imaging, Kathmandu, the first center with 3T MRI installed in Nepal. In MRI brain, routine sequences e.g. Axial images of T1 weighted, T2 weighted & FLAIR, Coronal images of T2, and Sagittal images of T1 weighted were obtained. Diffusion-Weighted Imaging (DWI) was obtained with a b value of 1000 and an ADC map. Susceptibility weighted Imaging (SWI) was also done in every case obtaining Magnitude and Phase images.

The data of MRI findings were collected from MRI reports and the stored images of the patients. Clinical notes of each patient were obtained from patient's file where referral & consent forms, technician's notes and photocopies of other relevant clinical informations were kept. Though many referral forms of the patients have mentioned features of concomitant high altitude pulmonary edema (HAPE), it was not taken in this study. MRI findings of the 49 patients evaluated were categorized into 3 groups according to the MRI features of HACE. Group A consists of patients with typical MRI findings of HACE in the given clinical background. Group B comprises MRI findings equivocal or likely HACE only in appropriate clinical situation. Their MRI scan showed T2 and FLAIR hyperintensity in deep and subcortical white matter and mostly without restricted diffusion. Location and signal changes are not typical of HACE and there is no MRI done before the mountaineering and in subsequent follow-up. Diagnosis of HACE in these MRI findings has been made correlating with the clinical features and excluding other similar conditions. Group C includes patients without any morphological abnormality or signal changes in the MRI brain. The data obtained were tabulated and analyzed accordingly by using SPSS version 21.

RESULTS

A total of 49 patients clinically suspected of HACE were taken in this study. Among them, males were slightly more in number than females.

Table 1. Age and sex distribution.

Age category (Years)	Sex		Total
	Male	Female	
<31	10 (20.41%)	10 (20.41%)	20 (40.82%)
31 - 40	7 (14.28)	4 (8.16%)	11 (22.44%)
41 - 50	6 (12.24)	4 (8.16%)	10 (20.40%)
>51	4 (8.16%)	4 (8.16%)	8 (16.32%)
Total	27 (55.10%)	22 (44.89)	49 (100%)

The age of the patients ranges from 19 to 67 years. The median age was 36 years (mean age = 36.55). This suggests that the AMS/ HACE was predominantly in young adults and it is statistically significant.

According to the groups defined in methodology, MRI findings were obtained as in the following table.

Table 2.MRI findings in patients in different Groups and different age categories.

Age Category	Group			Total	p-value*
	A	B	C		
< 31	3 (15.0%)	4 (20.0%)	13 (65.0%)	20	0.000
31 - 40	3 (27.3%)	1 (09.1%)	7 (63.6%)	11	
41 - 50	0 (00.0%)	5 (50.0%)	5 (50%)	10	
51+	0 (00.0%)	5 (62.5%)	3 (37.5%)	8	
Total	6 (12.25%)	15 (30.61%)	28 (57.14%)	49	

Out of the 49 patients with AMS and suspected HACE, 5 patients (10.20%) had MRI findings typical of HACE. These patients were trekkers rescued from around 4000-5500 meters (m). They were 21 to 40 years of age. 4 out of 6 had a history of loss of consciousness &

weakness. In MRI, high signal intensity was noted at the splenium of corpus callosum in 5 out of 6 patients which showed restricted diffusion in DWI. In these 5 patients, 3 patients had low signal intensity foci in SWI (in both Magnitude and Phase images) in splenium which were suggestive of microhemorrhage (Figure 1).

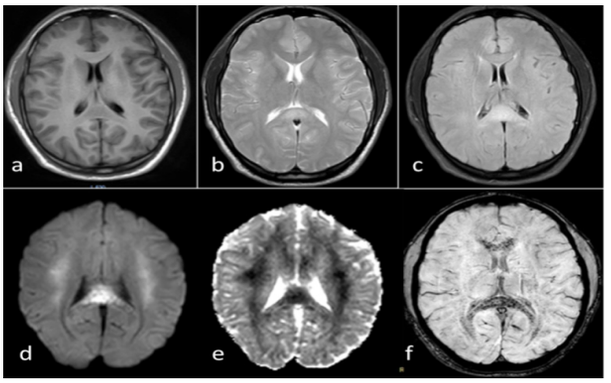

Figure 1. Typical MRI features of HACE with signal changes in corpus callosum displaying low signal in T1 (a) high signal intensity in T2 (b)and FLAIR (c) and restricted diffusion in DWI (d, e) with microhemorrhage in SWI (f).

One patient showed normal brain morphology and intensity in T1, T2, and FLAIR images (Figure 2) however, SWI showed innumerable variable-sized hypointense foci in Magnitude and Phase images in the corpus callosum, deep & subcortical white matter of bilateral cerebral hemisphere, and bilateral internal capsule. These features are in keeping with microhemorrhages. The patient was atrekker rescued from 4000 m with headache, dizziness, bilateral lower limb weakness with a history of loss of consciousness. These 6 out of 49 patients with typical MRI findings of HACE were categorized as group A in this study.

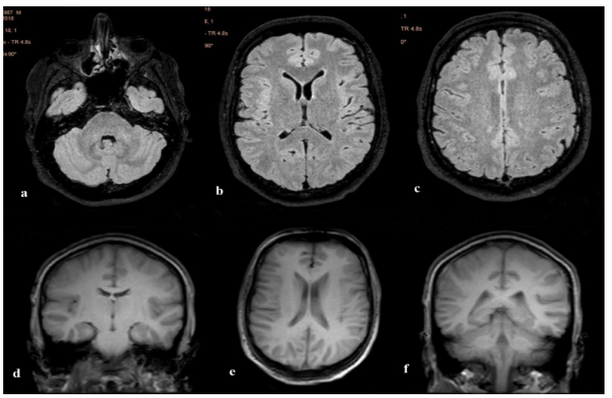

Figure 2. MRI brain, FLAIR (a,b,c) and T1 weighted images (d,e,f) show normal findings. This patient had multiple microhemorrhagic foci in brain in SWI (not shown).

15(30.61%) of 49 patients evaluated were heli-lifted from Dhaulagiri, Annapurna, and Everest Base regions. They were having various combinations of clinical symptoms of AMS (headache, dizziness, nausea, vomiting, blurring of vision) and 3 of them had ataxia or altered mental status. These are kept in group B in this study.

MRI of 8 of them showed T2 and FLAIR high signal intensity in the deep and subcortical white matter of bilateral cerebral hemisphere without restricted diffusion (Figure 3, 4). In 1 of these patients, T2 high signal intensity foci without restricted diffusion were noted in deep/ subcortical white matter in the right parietal lobe only. Solitary T2/ FLAIR high signal intensity focus seen in left frontal lobe and external capsule in 2 patients.

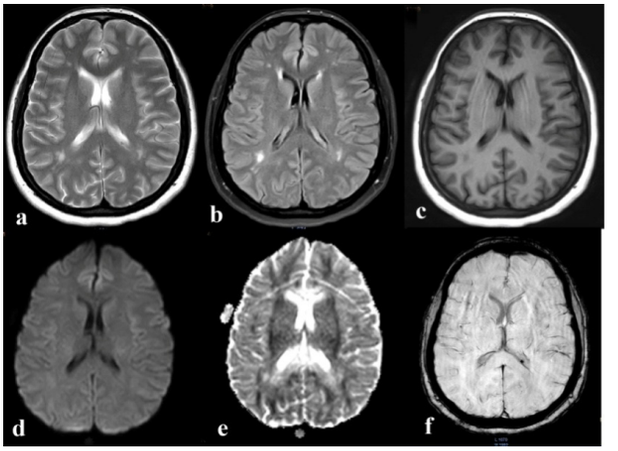

Figure 3. Multiple T2 (a) and FLAIR (b) high signal intensity foci in deep and subcortical white matter of both cerebral hemispheres which shows slight hypointensity in T1 (c). No restricted diffusion in DWI (d, e)and no evidence of microhemorrhage in SWI (f)

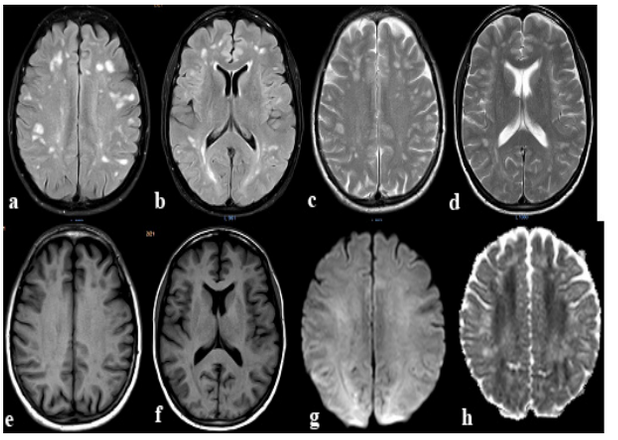

Figure 4. Brain shows multiple T2 (c,d)and FLAIR (a, b) high signal intensity foci scattered in deep and subcortical white matter of both cerebral hemispheres which show slight low signal in T1 (e, f) but no restricted diffusion (g,h).

2 (21 and 23 years) of the 15 patients had headache, dizziness, nausea, vomiting, blurring of vision, and a history of one episode of loss of consciousness & weakness. One of these two patients showed T2 high signal intensity area in the left temporal lobe and another had multiple T2 & FLAIR high signal intensity foci in the deep white matter of left frontoparietal lobes (Figure 5) without restricted diffusion. In these two patients only, we could see a decrease in size and number of the lesion in follow-up scans after more than 7 days.

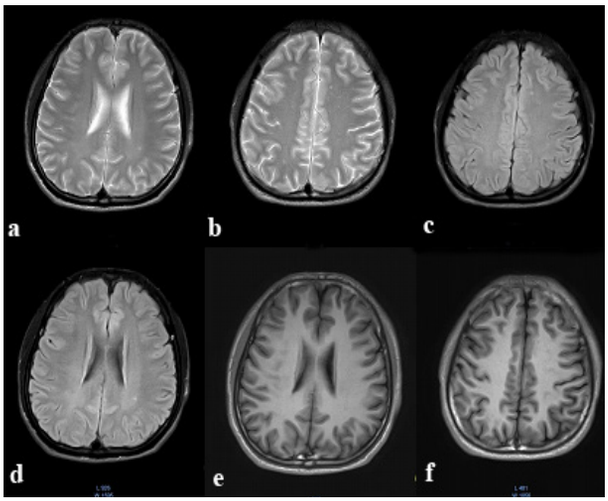

Figure 5. Decreased T2 (a, b), FLAIR (c, d) hyperintensity foci with T1 (e, f) iso to hypointensity seen in this follow up scan of a 23 year old patient with multiple T2 high signal intensity in white matter of left frontoparietal lobes in previous scan (not shown).

A 50 years female, normotensive and non-diabetic, was having a severe headache with a blurring of vision. On ophthalmological evaluation, findings were suggestive of high altitude retinopathy. In MRI, multiple T2 high signal intensity foci were noted in the deep white matter of bilateral frontal lobes.

MRI of one 42 years male patient evacuated from Dhaulagiri Base camp region with headache and dizziness showed multiple small areas of T2/FLAIR high signal intensity with restricted diffusion in the bilateral cerebellar hemisphere. Two small T2 high signal intensity oval lesions with restricted diffusion were also noted in the right frontal lobe at the deep and subcortical white matter. These features are suggestive of subacute lacunar infarcts.

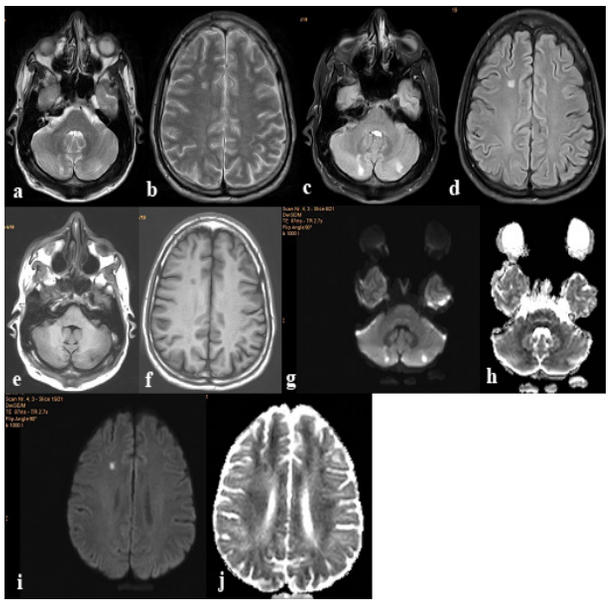

Figure 6. MRI brain in this suspected HACE with T2 (a,b) and FLAIR (c,d) high signal intensity foci in white matter of right frontal lobe and bilateral cerebellar hemispheres which shows restricted diffusion in DWI(g-j). These features suggest infarcts.

Out of 49, 28 patients (57.14 %) showed no abnormal morphology or signal changes in the MRI scan and kept in group C in our study. No evidence of restricted diffusion and no abnormality were seen in the SWI of the brain. Out of these 28 patients, 15 were female. All were taken to the hospital from high altitude (up to 5000 m) with various symptoms of AMS and suspected HACE. In AMS, headache is the predominant symptom in this group which was presented in 25 out of 28. It was severe in 6 and 1 had an extreme headache (pain scale of 10/10). 13 patients had dizziness, 6 had nausea and vomiting and 5 had a fainting attack. Though normal MRI brain findings, 4 of the patients in this group had features of HACE as lassitude and altered mental status.

DISCUSSION

CT may show cerebral edema however MRI can delineate subtle signs of brain edema. Low Tesla MRI (<1 Tesla) may not show the specific features of HACE like microhemorrhage which needs high tesla MRI (1.5-3.0 Tesla). For those reasons high tesla MRI is the choice of investigation.

This study showed slight male preponderance (54% male) though both males and females are equally susceptible to AMS. The median age of the patients was 36 years. It was a convenient sample but indeed it was in keeping with the high-altitude medical literature which seems to support the younger age group being more susceptible to altitude illness.

The MRI imaging features divided into 3 groups as described were found in other studies as well.5 out of 6 patients (group A) with typical clinical features of HACE showed high signal intensity at the splenium of corpus callosum and restricted diffusion in DWI. Evidence of microhemorrhage in splenium was noted in 3 of these patients.

Matsuzawa et al mentioned slightly increased T2 signal of white matter in the sickest 4 of 7 subjects with AMS in his book in 1992.[9] Hackett et al evaluated MRI of 9 patients in 1998 with HACE.[10] He demonstrated strikingly increased T2 signal in the corpus callosum, particularly in the splenium, with additional involvement in the centrum semiovale in 7 out of 9 patients. Findings in only T2 and Proton density images were presented and no FLAIR, DWI, and Gradient images/SWIwere mentioned. Vasogenic edema was considered the underlying pathology. A study published in 2019 by Hackett et al[11] showed reversible restricted diffusion in the corpus callosum with a predilection for the splenium in 7 patients out of 8 evaluated. He termed it cytotoxic edema in this study. Stakey et al in 2017 stated that corpus callosum with very short perforating vessels lacking adrenergic tone become vulnerable to hypoxia-induced vasodilatation and its autoregulatory failure with resultant hyperperfusion. The cytotoxic edema in the corpus callosum and particularly the splenium is related to cytokinopathy.[12]

Kühn et al[13] studied low-altitude (< 500m) native healthy individuals exposed to high altitudes (4554 m). In their study, 1 individual out of 9 showed cytotoxic edema by the high signal intensity in T2 and increased signal intensity in DWI with decreased ADC value.

One of these patients in Group A of this studyshowed normal brain in T1, T2, and FLAIR sequences however SWI showed evidence of innumerable variable size microhemorrhages in the corpus callosum, deep & subcortical white matter of bilateral cerebral hemisphere, and bilateral internal capsule. This patient was a trekker rescued from 4000 m and had obvious clinical features of HACE. These findings further corroborated the brain MRI features of HACE.

In the 1970s, Dickinson et al[14] studied the autopsy of 6 fatal cases of HACE. All 5 of 6 cases showed edema in the brain. One of his cases showed no edematous brain but had small hemorrhages and petechiae in the subcortical white matter of the cerebrum, corpus callosum, pons, and cerebellum along with congestion of vessels which was similar to one of our cases. Hackett et al[11] in SWI sequence of MRI also found microhemorrhage (termed microbleed) in 6 out of 8 patients with HACE as 'black pepper-like appearance in white matter, more in the corpus callosum.

In a study by Kottke et al[15], they found microhemorrhages in splenium in 3 of 15 climbers who went to 7000 m and had mild to moderate AMS but did not have HACE or HAPE.

Our MRI findings are compatible with the findings in the above MRI studies of HACE by Matsuzawa, Hackett et al, Kühn, Dickinson, and Kottke et al.[9,10,13,14,15] Therefore, the MRI findings in this group A were typical for HACE.

The patients in group B showed multiple T2 & FLAIR high signal intensity foci in the deep and subcortical white matter of uni or bilateral cerebral hemispheres including basal ganglia in various combinations. We have no prior or almost no serial MRI after the trek to compare except in 2 patients who showed a decrease in size and number of T2 and FLAIR high signal intensity foci in follow-up scan. No other known causes of white matter hyperintensity were noted.

Garrido et al[16]studied MRI (in GE 1.5 T) of 26 patients who returned from high mountains (>7000) between 26 days to 36 months after returning to sea level. They showed areas of persistent high signal intensity in 5 patients (19.2%) with a history of AMS and HACE. The change was at the bilateral and unilateral periventricular white matter.

Fayed et al[17]studied MRI in climbers of different high mountains (4810-8848 m). MRI of 12 of 13 amateur climbers of the expedition to Everest and 4 out of 8 subjects in an expedition to Aconcagua showed multiple subcortical lesions on T2-weighted MRI.

Hackett et al[10] demonstrated reversible high signal intensity in the corpus callosum, centrum semiovale, and in periventricular white matter and resolution of the findings in follow-up scan. Same leading author, Hackett et al[11] studied clinically known cases of HACE and delineated T2 and FLAIR high signal intensity in subcortical and periventricular white matter in 3 cases.

Matsuzawa, Hackett, Kühn, Dickinson, Kottke, Garrido, and Fayed et al,[9,10, 13- 17] all mentioned the presence of T2 high signal intensity in white matter. Therefore, given recent evacuation from high mountains and the presence of T2 high signal intensity in white matter, these changes in MRI could be lesions in the spectrum of MR findings in HACE.

A female patient of 50 years in this group had high altitude retinopathy along with multiple T2 high signal intensity in the deep white matter of bilateral frontal lobes. Retinal hemorrhages present in up to 60% of patients with HACE though it may also be found in asymptomatic persons at high altitudes.[18] Retinal capillary leakage may be the only finding in a patient with HACE.[19] She might be having milder changes in the spectrum of MR brain findings and retinopathy of HACE.

A male patient of 42 years in this group showed features of multiple lacunar infarcts in the bilateral cerebellar hemisphere and right frontal lobe at the deep and subcortical white matter. Back in 1983, Dickinson et al[14] showed hemorrhagic cerebral infarcts in one of his 6 patients in brain autopsy. Hackett et al[11] also showed lacunar infarcts in the globus pallidi and left frontal subcortical white matter. Their relation to HACE is not so clear. However, it needs more study with more numbers of patients to better evaluate the occurrence and pathophysiology of lacunar infarct in HACE.

57.14% (28) patients included in group C showed no abnormal morphology or signal changes in MRI scan. All were taken to the hospital from a high altitude (up to 5000 m). Garrido et al[16] showed normal MRI findings in 14 (54%) high altitude climbers (>7000 m) without oxygen with features of HACE. He had stated that the findings didn't significantly correlate with age, altitude, and length of exposure to altitude.

Hackett et al[10] observed that the 2 patients with features of HACE did not demonstrate the MRI abnormalities. They considered it due to less exposure to altitude, prompt evacuation, and less activity aggravating the cerebral capillary pressure in them. Kottke et al[15] didn't find MRI lesions in 12 of 15 climbers. Kühn et al[13] found no focal lesion in MRI in 7 out of 9 patients with the same height and duration of ascent in high altitude.

These findings suggest that there is wide variation in MRI findings which do not exactly correlate with clinical findings of AMS and HACE in high altitude climbers. Almost all climbers with mild to moderate AMS and many climbers with HACE may have normal MRI findings. The normal finding may be due to the short time of high altitude exposure, prompt evacuation to the low land, and acclimatization capacity of a person.

This condition is infrequent, only occurring in high mountains with seasonal variations and taking a long time for patients to get to the medical institutions with MRI facilities. Therefore, the earliest changes may have been missed. The patients had only one MRI scan, therefore, serial subsequent changes could not be recorded. Subsequent clinical development and outcome has not been included in this study.

CONCLUSIONS

MRI brain is an essential investigation for a complete evaluation of the presence and extent of the pathology in the brain in moderate to severe AMS and HACE. Typical MRI features of cytotoxic edema in the corpus callosum (particularly in splenium) and microhemorrhage in the patients with HACE in our study further support the findings in other similar studies. SWI is the important sequence in MRI to identify microhemorrhage.

T2 white matter hyperintensities, reversible or persistent could be seen in deep, subcortical, or periventricular locations, isolated or in various combinations, unilateral or bilateral, irrespective of features of AMS or HACE. Alternative conditions of white matter hyperintensities should also be considered. Lacunar infarcts noted in this and various other studies could be one of the associations which might need further study. Normal MRI of the brain is not infrequent.

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CONFLICT OF INTEREST

No conflict of interest.

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