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Original Research

Magnetic Resonance Neuroimaging Findings in High-altitude Cerebral Edema (HACE) and Probable Correlation with its Temporal Evolution and Pathogenesis.

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Abstract

Background: High-altitude illness (HAI) is a spectrum continuum ranging from innocuous high-altitude headache (HAH) to severe, potentially fatal high-altitude cerebral edema (HACE) with acute mountain sickness (AMS) and high-altitude pulmonary edema (HAPE) in the middle of the gamut. MRI brain findings in such patients have prognostic implications, especially the diffusion and susceptibility-weighted imaging.
Methodology: Twenty-one devotees visiting a high-altitude cave temple, in whom there was a clinical suspicion of high-altitude cerebral edema after the ascent, were included in this study. All the patients met the criteria for diagnosis of acute mountain sickness (AMS) as well as HACE. MRI brain was done in all 21 patients with special emphasis on diffusion and susceptibility-weighted imaging.
Results: Diffusion restriction with T2/FLAIR hyperintensity was present in the splenium of the corpus callosum in all 21 patients. Other sites involved were centrum semiovale and deep white matter (90.5%), middle cerebellar peduncles (66.7%), and posterior limb of the internal capsule (57%). SWI revealed multiple tiny cerebral microbleeds in splenium, deep white matter, and middle cerebellar peduncles.
Conclusion: This study suggests the evolution of diffusion restriction, T2/FLAIR hyperintensity, and cerebral microbleedsin the splenium of the corpus callosum and white matter in HACE corresponds well with the temporal evolution of cytotoxic, ionic,and vasogenic cerebral edema underpinning the role of brain water dyshomeostasis central to the pathogenesis of HACE.

Keywords: High-Altitude Illness; Amarnath Yatra Pilgrims; High-Altitude Pulmonary Edema; High-Altitude Cerebral Edema; Cerebral Microbleeds; Susceptibility Weighted Imaging.

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Introduction

High altitude illness (HAI) is a spectrum continuum ranging from innocuous high-altitude headache (HAH) to severe, potentially fatal high-altitude cerebral edema (HACE), with acute mountain sickness (AMS) and high-altitude pulmonary edema (HAPE) in the middle of the gamut [1]. The shared etiology is the low oxygen level at high altitudes, with the clinical outcome subservient to patients, altitude and acclimatization-related factors [2]. The golden adage among climbers that "HAI spectrum can occur in anyone, at any altitude, at any time with any level of acclimatization" still holds true [3]. HACE is the least common but most severe end-stage form of HAI, which can rapidly progress to coma and death if not diagnosed and managed promptly [4]. Although HACE is a clinical diagnosis, the growing availability and use of brain MRI in these patients not only clinches the final diagnosis but also provides a sneak peek into the etiopathogenesis of the same. We present MR imaging findings in a series of such patients who ascend 3000-4000m altitude to visit a world-famous and revered holy cave temple "Amarnath" located in the heart of the Himalayas [5].

Methodology

It is an observational single-center study carried out over a span of three non-consecutive years. The pilgrimage is scheduled in the months of July and August. Informed consent was taken from all the patients or their attendants. Institutional ethical clearance was not required for this observational study. Twenty-one devotees in whom there was a clinical suspicion of high-altitude cerebral edema were transported back to the base camp and air-lifted to our tertiary care hospital. All the patients met the criteria for diagnosis of AMS as well as HACE. Complete lab work-up was done in the form of complete and differential blood count, blood sugar, arterial and venous blood gas analysis, renal and liver function test, and chest X-ray. Lumbar puncture and HRCT chest were performed wherever indicated. MRI brain was done in all 21 patients using 1.5 T MRI (Magnetom, Avanto, Siemens Medical System) with a standard head coil. The imaging protocol included all the standard MRI brain protocol sequences, especially:

Axial T2 weighted (T2W) fast spin echo sequence (TR / TE 3500 ms /110 ms; slice thickness 5 mm & field of view FOV 230 mm).

Axial FLAIR sequence (TR / TE/inversion time 8000 ms / 108 ms / 2500 ms; slice thickness 5 mm & FOV 230 mm).

Diffusion-weighted imaging (DWI) using an axial echo-planar spin echo sequence (TR / TE 3000 ms/ 87 ms; 5 mm section thickness; 230 mm x 230 mm FOV. DW images and ADC maps were obtained using b values of 0, 500 & 1000 s mm^2.

Susceptibility weighted imaging (SWI) in the axial plane (TR / TE 49ms / 40 ms; slice thickness 2.5mm & FOV 230 mm).

In addition, MR venography was done if there was high suspicion of dural venous sinus thrombosis.

Results

All the patients were aged 40-68 years, with eighteen being men and three females. No devotee had previous high-altitude experience belonging predominantly to the Indo-Gangetic plains (300-600 m above sea level). The predominant neurological symptom was confusion and altered mental status in 100 % of patients (21/21), followed by ataxia (85.7 %; 18/21). A variable degree of respiratory alkalosis was present in all the patients. Severe hypoxemia was seen in 90.5 % (19/21). The clinical diagnosis of HAPE was seen in 85.7 % (18/21), which was confirmed by chest X-ray/HRCT. Thirteen patients required intubation during hospitalization (62%). The average hospital stay was 9.3 days. Two patients

(9.5 %) expired - one on the 5th day of admission, and the death of another patient was telephonically confirmed 14 days post-discharge from the hospital. The MRI findings of these patients are presented in

Table 1: MRI findings in brain in HACE patients in our study.

S. No	MRI findings in brain (A)	Number of patients (n); Percentage (%)	Subset of patients with MRI findings in brain (A) with	
			Cerebral Microbleeds	Diffusion Restriction
1.	**T2/FLAIR hyperintensity in Splenium of Corpus Callosum**	21 (100)	19/21 (90.5)	21/21 (100)
2.	**T2/FLAIR hyperintensity in subcortical white matter (Centrum Semiovale)**	19 (90.5)	16/19 (84.2)	15/19 (79)
3.	**T2/FLAIR hyperintensity in middle cerebellar peduncle**	14 (66.7)	11/14 (78.5)	11/14 (78.5)
4.	**T2/FLAIR hyperintensity in posterior limb of internal capsule**	12 (57.1)	8/12 (66.7)	8/12 (66.7)
5.	**T2/FLAIR hyperintensity in Globus pallidus**	1 (4.8)	0/1 (0)	1/1 (100)
6.	**Lobar hematomas**	0	0	0
7.	**Features of dural venous sinus thrombosis**	0	0	0

Discussion

HACE is a potentially lethal condition that is often described as a severe form of end-stage acute mountain sickness. Incidence of HACE has been reported as 0.5-1 % at altitudes of 3500-4000 m [6]. Risk factors include a prior history of HAI, rapid accent, inadequate acclimatization, a continuation of ascent despite symptoms, extreme altitudes, and severe physical exertion [7]. HACE in isolation is a rare phenomenon, but the absence of signs and symptoms of concomitant AMS /HAPE does not rule out the absence of HACE [8]. The devotees to the Amarnath Cave in our study belonged to areas only 200-600m above sea level with an ascent of 3000-4000m altitude over a period of few days [9]. The most common neurological symptoms reported were altered mental status, followed by ataxia [10]. Patients usually suffer from symptoms of high-altitude headache and AMS before transitioning to HACE. Ataxia is

reported as the earliest symptom of HACE. Patients usually have symptoms of concomitant HAPE [11]. Untreated, the disease rapidly progresses to global encephalopathy, coma, and death due to brain herniation [12].

It is worthwhile to mention the probable underlying pathogenesis of HACE before discussing the neuroimaging features in our study. The sequential or simultaneous interplay of neuro-hormonal, myogenic, and hemodynamic responses due to rapid ascent-induced hypoxia, coupled with individuals' sensitivity to low oxygen levels, hypocapnic cerebral response, and cerebral buffering capacity, determines the severity of HACE [13]. At the heart of the AMS / HACE spectrum lies the brain water dyshomeostasis determined by various types of cerebral edemas [7, 13].

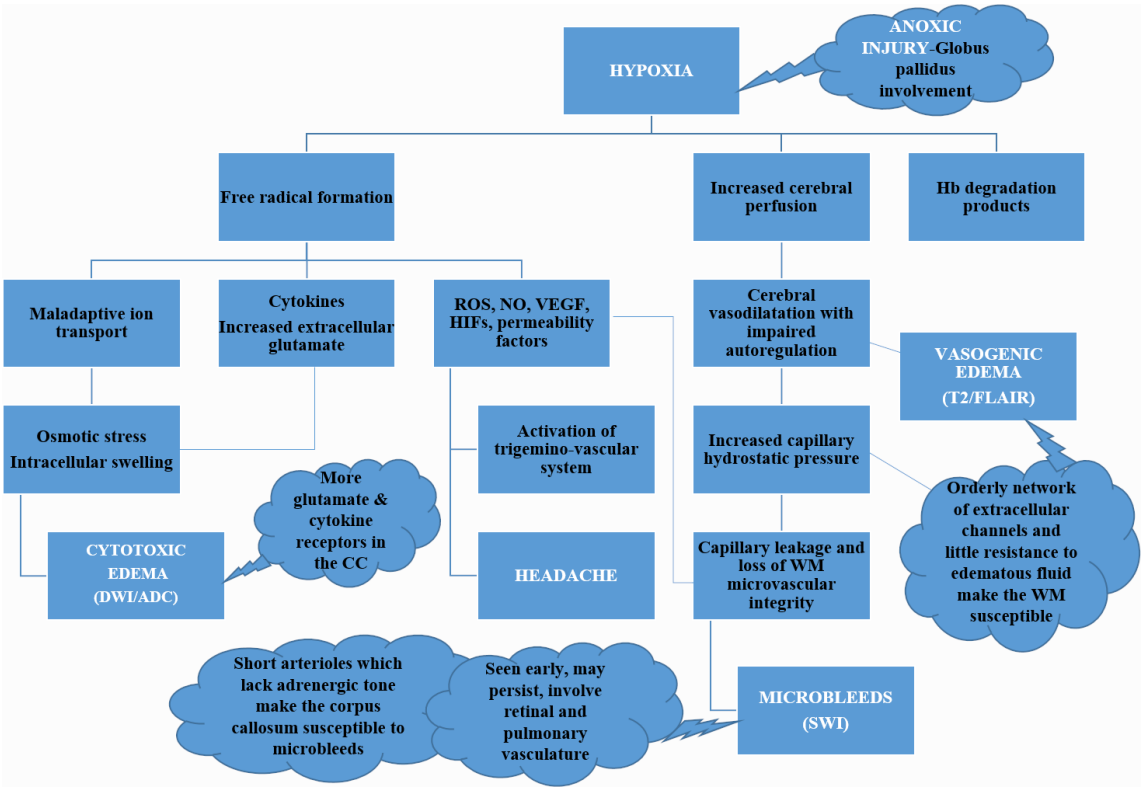

Figure 1: Flowchart depicting the pathogenesis and corresponding imaging correlates in High Altitude Cerebral Edema.

Figure 1: Represents the pathogenesis in the flowchart pattern. The earliest response to hypoxia is cerebral vasodilatation, triggering the trigeminal vascular system, which explains the high-altitude headache in these patients [7]. Simultaneous subtle energy depletion due to hypoxia causes intracellular cytotoxic swelling due to the failure of transmembrane ion extrusion mechanisms, resulting entry of ions and subsequently water into the cells [14]. This explains the earliest finding of diffusion restriction seen in patients in our study. The splenium of corpus callosum showed restriction in all the patients, while it ranged from 78% in centrum semiovale to 58% in the posterior limb of the internal capsule

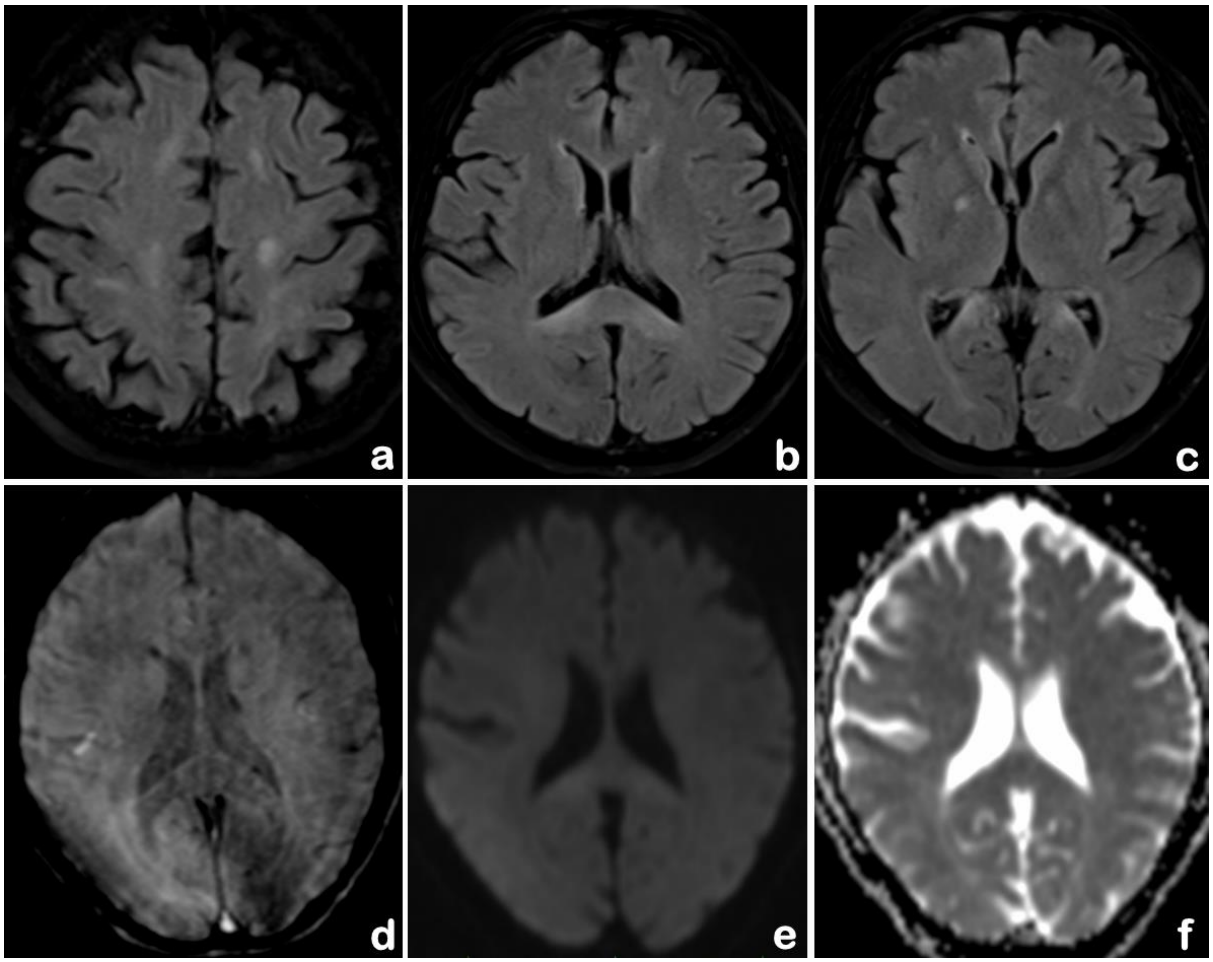

Figure 2: Axial FLAIR images (a-c) show ill-defined, patchy asymmetric hyperintensities involving the subcortical white matter of the frontal lobes (a) and corpus callosum splenium (b). Discrete hyperintense foci are seen in the anterior part of the Globus pallidi (c). Few microbleeds are noted in the corpus callosum splenium on the axial SWI image (d). Note that the diffusion restriction across the corpus callosum on the diffusion weighted trace image (e) and ADC map (f) is not as striking as in subsequent figure 3. The white matter changes are patchy and asymmetric unlike figure 3. This was a mild case of High-altitude cerebral edema where the patient recovered without any sequelae.

(**Figure. 2**). This predilection for splenium of corpus callosum can be explained by a greater number of glutamate and cytokine receptors which mediate deranged transmembrane ion transport causing cytotoxic edema and restricted diffusion of water molecules [15]. The other contributing factor may be the nature of the blood vessels supplying the corpus callosum. The vessels are short perforating vessels that lack adrenergic tone, making them vulnerable to hypoxia-induced vasodilatation and subsequent autoregulation failure and hyper-perfusion [1].

There is no increase in brain water content by this time, and blood blood-brain barrier (BBB) is intact. The ion deficit in the cerebral extracellular space triggers ion and water movement across the intact BBB due to trans-vascular osmotic gradient, resulting in ionic edema [14]. Continuing hypoxia, endothelial dysfunction, and vascular injury generate reactive oxygen species along with hypoxia-inducible factors (HIF) regulated vascular permeability factors and systemic inflammatory markers, causing disruption of the BBB with protein and erythrocyte-rich ultra-filtrate, causing vasogenic edema [16,17]. What underpins this cascade is still speculative, but the result is increased or fluctuating intracranial pressure,

further white matter microvascular integrity loss, cerebral microbleeds, and severe HACE [18]. This pathology may be compounded by HAPE seen simultaneously in 85 % of HACE patients while only 15% of HAPE patients develop HACE [6]. The vasogenic/ionic edema explains the predominant T2/FLAIR hyperintensity

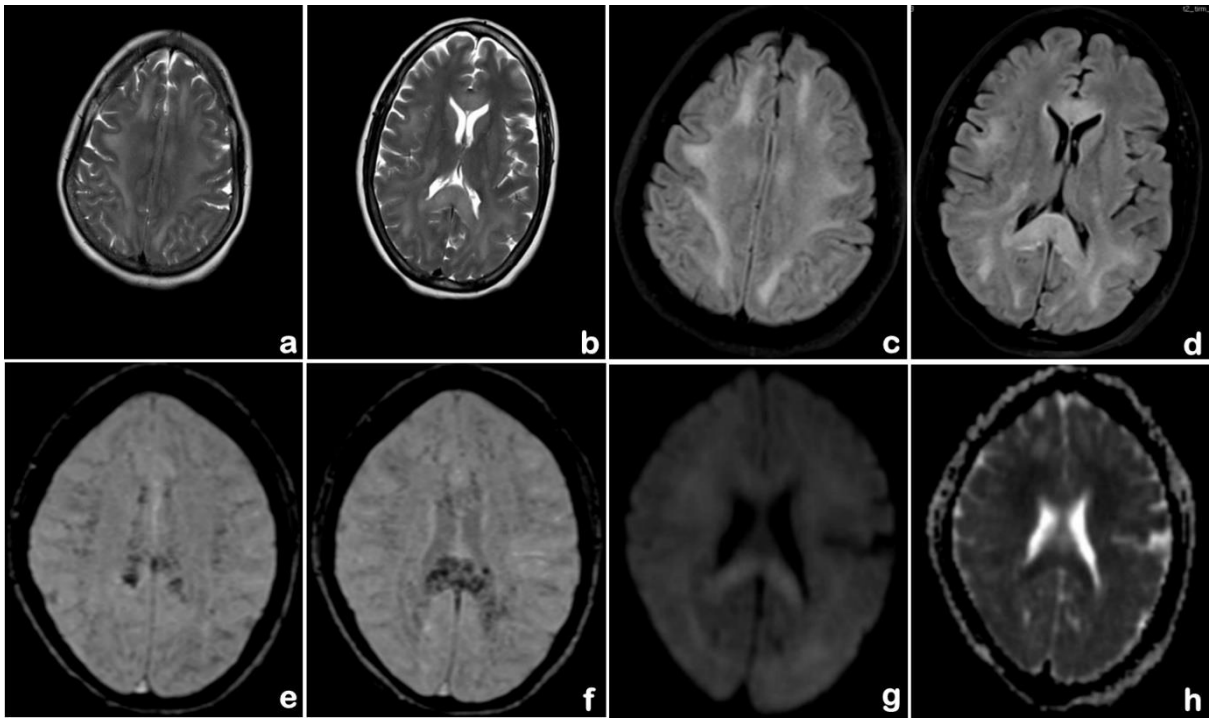

Figure 3: Axial T2 weighted (a, b) and FLAIR images (c, d) show symmetric, confluent hyperintensity involving the subcortical white matter in the frontal, parietal and occipital lobes extending across the genu and splenium of the corpus callosum. Hyperintensity is also noted in the posterior limb of the internal capsule on both sides. Multiple microbleeds are seen in the subcortical white matter and splenium of the corpus callosum on axial susceptibility weighted images (e, f). Diffusion weighted trace image (h) and corresponding ADC map (g) show diffusion restriction across the splenium of the corpus callosum. These imaging findings are typical of high-altitude cerebral edema in the appropriate clinical setting.

(**Figure 3**) seen in the splenium of the corpus callosum (100 %), subcortical & deep white matter (84 %), middle cerebellar peduncles (67 %), and posterior limb of the internal capsule (57%). The distribution was confluent and symmetrical in the centrum semiovale and patchy in the posterior limb of the internal capsule and middle cerebellar peduncles. SWI showed cerebral microbleeds

(**Figure 3**) in the splenium (100 %), white matter (79%), middle cerebellar peduncles (78.5 %), and the posterior limb of the internal capsule (66.5%). The microbleeds were multiple, giving a classic black pepper-like appearance on SWI. The putative mechanism appears disruption of BBB and loss of white matter microvascular integrity [18]. No correlation of cerebral microbleeds with white matter T2 / FLAIR hyperintensity or diffusion restriction was seen.

It is notable to mention that one patient in our study showed symmetrical T2 / FLAIR hyperintensity involving Globus pallidus with diffusion restriction (**Figure 4**).

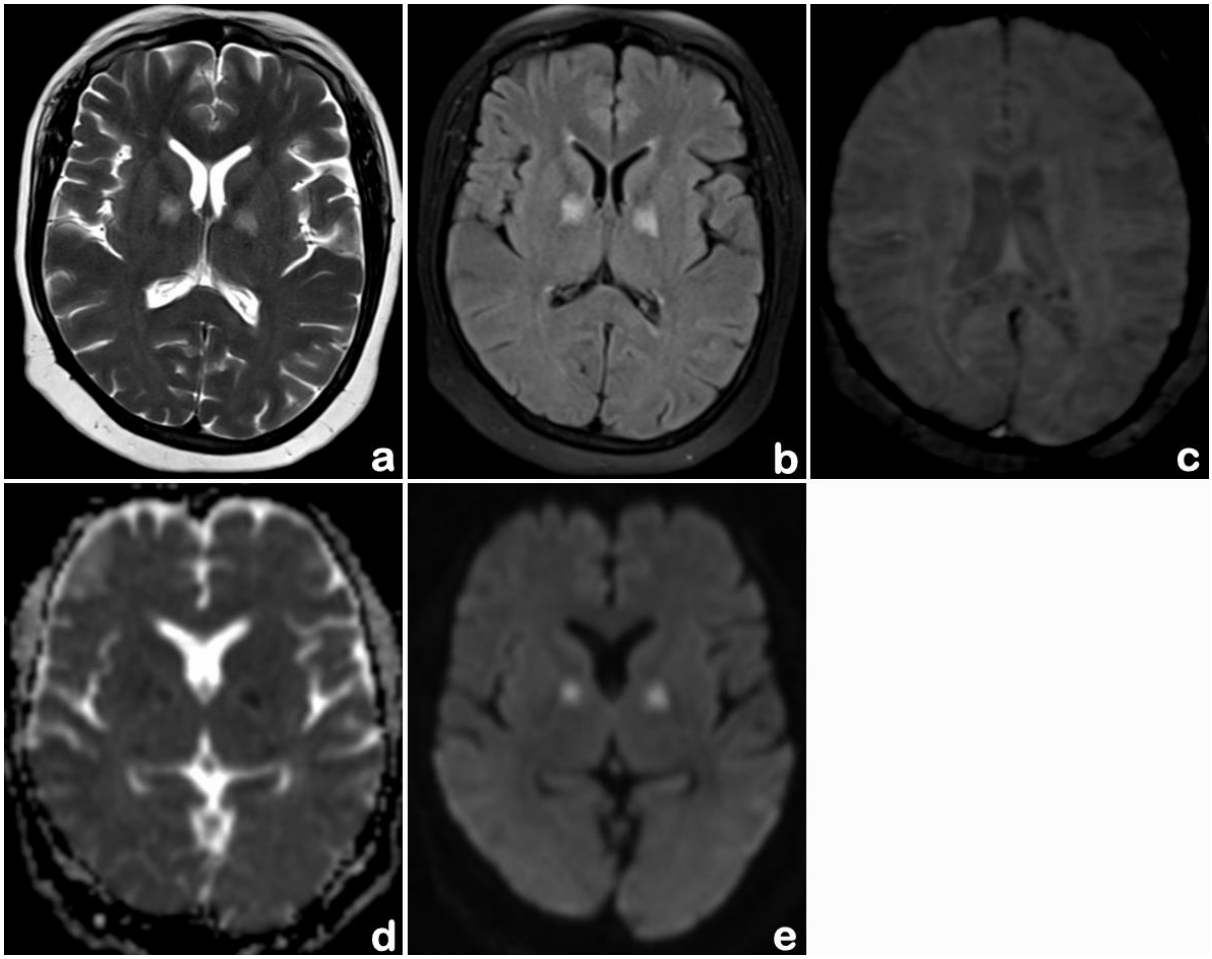

Figure 4: Axial T2 weighted (a) and FLAIR image (b) show symmetric hyperintensity involving the Globus pallidi with striking diffusion restriction on the diffusion weighted trace image (e) and corresponding ADC map (d). Note the subtle hyperintensity in the corpus callosum splenium on the T2 weighted (a) and FLAIR image (b) with microbleeds on SWI (c). Involvement of the Globus pallidi is suggestive of a hypoxic injury in a background of HACE.

The patient had severe HAPE, explaining the finding secondary to severe hypoxic-ischemic insult. The patient also had T2 / FLAIR hyperintensity with cerebral microbleeds in the splenium of the corpus callosum & centrum semiovale, explained by background change of HACE. Two patients died in our study (9.5%), including the one who had Globus pallidus involvement. Differential diagnoses in the high-altitude setting include hypothermia, hypoglycemia, hyponatremia, carbon monoxide poisoning, and dural venous sinus thrombosis [19]. These can be differentiated by appropriate clinical, laboratory, and imaging evaluation.

Our study had several limitations. The most significant was reliance on one-time imaging without follow-up imaging. The MRI used was 1.5T, which underestimates the cerebral micro-bleed burden. There was no method to objectively quantify the cerebral micro-bleed burden, correlate it with the clinical severity of the disease, and predict the imaging markers of severe disease. New techniques like diffusion tensor imaging and fractional anisotropy, as well as MRI techniques with high-velocity sensitivity, may better explain the brain water dyshomeostasis that underpins the pathogenesis of HACE [20, 21]. Neuroimaging is partially able to explain the sequence of appearance of various cerebral edemas associated with HACE; however, the role of perivascular cerebral tunnels (glymphatic system), aquaporin (AQP4) channels, and

venous outflow obstructions is still an area of active research [22,23]. Further studies are needed to validate/refute their role in HACE.

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