# Chapter 11
# Management of High-Altitude Cerebral Edema and High-Altitude Pulmonary Edema

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## Case Presentation

A 25-year-old male with no prior co-morbidities, residing at 300 m above the sea level decided to go to Annapurna circuit for vacation. On the fifth day of his ascent to Thorong-la pass which is at 5416 m above the sea level, he started having generalized headache associated with vertigo, nausea, and vomiting, progressively worsening over the next 24 h when he was observed to have an unsteady gait by his friends. Within the next few hours, he was found to be drowsy and not responding to verbal commands. He was then heli-rescued within the next few hours to our hospital at Kathmandu. On arrival to our hospital, he was found to have a pulse of 96/min, blood pressure of 142/72 mm Hg, respiratory rate of 32/min and $SpO_2$ 77% in ambient air. Neurologically he was found to be disoriented with non-coherent talks and had bilateral positive Babinski sign. Chest examination revealed bilateral basal crepitations. Other systemic examination was normal. Fundus examination revealed papilledema.

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*Q1: What are your differentials from the history and findings of physical examination?*

A:

1. Acute Mountain Sickness/High altitude cerebral edema/High altitude pulmonary edema
2. Right sided stroke
3. Sub-arachnoid hemorrhage
4. Central nervous system infections
5. Hypothermia
6. Seizures
7. Transient Ischemic attack
8. Brain tumor
9. Myocardial infarction
10. Pulmonary embolism
11. Pneumonia with MODS
12. Hyperventilation syndrome

*Q2: What further tests would you like to do?*

A: **Lab investigations - helpful**

1. Random blood sugar level
   - Hypoglycemia and exhaustion may be the cause of low GCS
2. ABG
   - With increasing altitude, there is a decrease in atmospheric pressure, resulting in a lower $PAO_2$ and, consequently, a lower $PaO_2$, as explained by the alveolar gas equation
     - $PAO_2 = FiO_2\ (Patm - PH_20) - (PaCO_2/R)$
   - Thus, a low $PaO_2$ is expected at such a high altitude of Thorong La Pass, as is low $SpO_2$. However, A-a gradient will help us distinguish if pulmonary edema is present.
   - Low $PaO_2$ and normal A-a gradient implies hypoxia due to high altitude, whereas, Low $PaO_2$ and elevated A-a gradient implies pulmonary edema
   - Mild respiratory alkalosis may be present due to hyperventilation secondary to hypoxia
3. CBC
   - Haemoglobin concentrations may be high due to a fall in the plasma volume as a result of dehydration
   - White blood cell count may be elevated in the setting of HACE
4. RFT
   - To rule out kidneys as a cause of dys-electrolytemias or altered sensorium

5. LFT
   - To rule out liver as a cause of altered sensorium
6. ECG and bedside ECHO
   - To rule out myocardial infarction, left ventricular dysfunction and assessment of volume status
7. Chest X-ray
   - To rule out pulmonary edema and possible pneumonia
8. Non contrast CT head
   - To rule out other causes of fall in GCS

**Investigations – less helpful** (but may be needed if first line of investigations are not helpful in establishing the diagnosis or the patient does not respond to the initial treatment)

1. Lumbar puncture
   - To rule out CNS infections
2. EEG
   - To rule out seizure as a cause of altered sensorium and possible toad's palsy
3. CT angiography with venogram
   - If there is suspicion of Cerebral venous sinus thrombosis as a cause of altered sensorium
4. MRI brain
   - To rule out other pathologies as a cause of altered sensorium

His hematological and biochemical parameters were within normal limits (hemoglobin 14 g/dL, total leucocyte count 10,500/μL, differential leucocytes polymorphs 65%, lymphocytes 32%, blood sugar random 100 mg/dL, urea/creatinine 28/1.0 mg/dL, total/direct bilirubin – 1/0.2 mg/dl, SGOT/SGPT-34/42 mg/dl, protein/albumin- 6.3/4.6 gm/dl, cultures negative). ECG showed normal sinus rate and rhythm without ST changes. Chest radiograph revealed fluffy perihilar opacities in bilateral lung fields suggestive of pulmonary edema (Fig. 11.1). Optic nerve sheath diameter (ONSD) was 6 mm in the right eye and 6.2 mm in the left eye. Non-contrast CT scan (NCCT) of the brain showed diffuse cerebral edema involving white matter of bilateral cerebral hemispheres with accentuation of grey–white matter differentiation, mass effect in the form of the effacement of the overlying sulci and compression of the lateral ventricles and third ventricle (Fig. 11.2). EEG was normal.

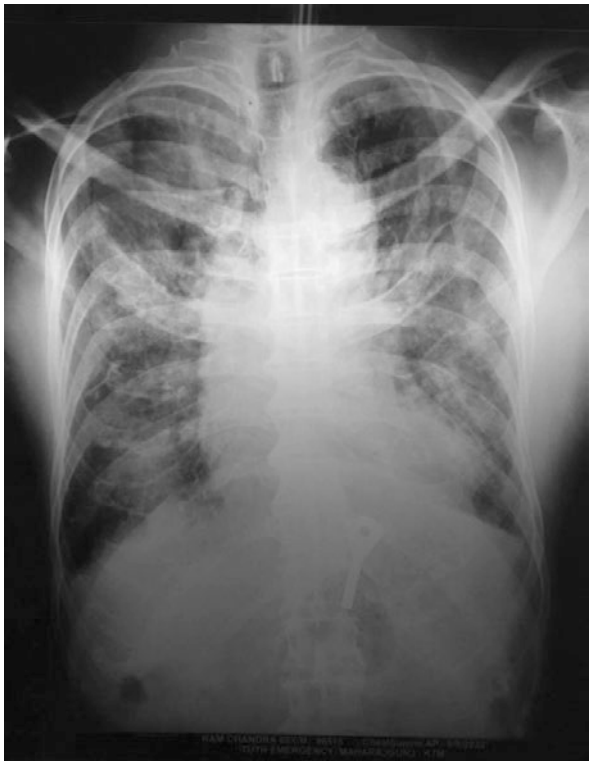

**Fig. 11.1** Chest radiograph revealing fluffy perihilar opacities in bilateral lung fields suggestive of pulmonary edema

*Q3: What is your provisional diagnosis?*

A: High altitude cerebral edema with high altitude pulmonary edema.

*Q4: How did you come to this conclusion?*

A: Unacclimatized individuals are at risk of high-altitude illness when they ascend rapidly to altitudes above 2500 m [1]. HACE has been reported at around 2500 m in patients with concurrent HAPE [2]. The patient is young, without prior co-morbidities, who had been residing at an altitude of 300 m and has rapidly ascended to an altitude of 5416 m in five days. He has presented initially with clinical features of acute mountain sickness viz., headache, nausea and vomiting which has progressed to signs of HACE viz., ataxia and progressive decline of mental function and consciousness. This transition takes time ranging from 12 h to three days, however HACE develops faster in patients with HAPE, most likely as a result of severe hypoxemia as seen in this case [3]. The presence of papill-edema in the eyes and positive Babinski sign has been reported in HACE [4]. Similarly the findings of non-contrast CT head has further supported the diagnosis. The findings of hypoxia and chest x-ray points out towards acute pulmonary edema. There are negative findings of hematological and biochemical parameters along with negative ECG and EEG findings to suggest alternative diagnosis. Thus, the history, clinical and investigations points towards the diagnosis of HACE and HAPE.

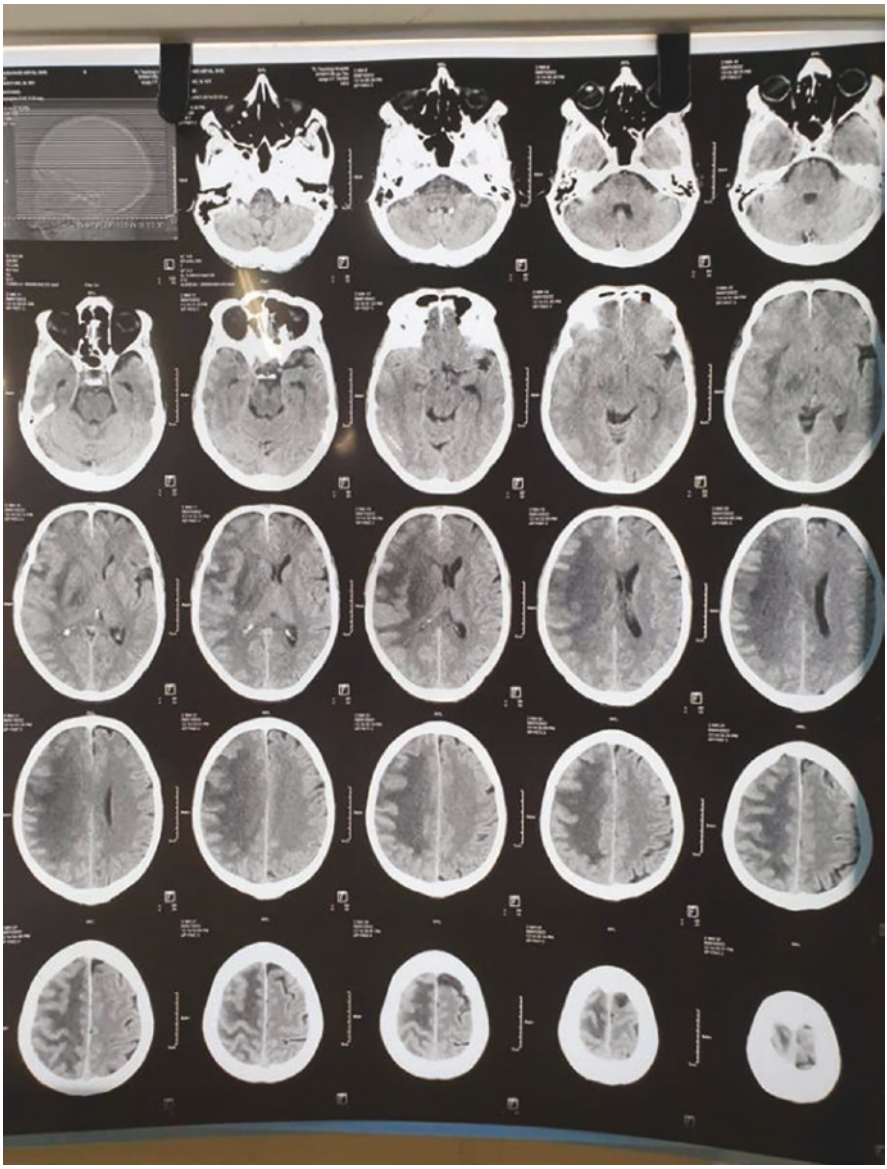

**Fig. 11.2** Non-contrast CT scan (NCCT) of the brain showed diffuse cerebral edema involving white matter of bilateral cerebral hemispheres with accentuation of grey–white matter differentiation, mass effect in the form of the effacement of the overlying sulci and compression of the lateral ventricles and third ventricle

*Q5: Do you know of any scoring systems to identify Acute Mountain Sickness/ HACE/ HAPE?*

A: Lake Louise AMS Score has been the most widely used scoring system for research (Table 11.1). Other tools to diagnose AMS includes Acute Mountain

**Table 11.1** The Lake Louise Acute Mountain Sickness Scoring System [2] [8]

| Symptoms | Severity | Points |
|---|---|---|
| Headache | None at all | 0 |
| | Mild headache | 1 |
| | Moderate headache | 2 |
| | Severe headache, incapacitating | 3 |
| Gastrointestinal symptoms | Good appetite | 0 |
| | Poor appetite or nausea | 1 |
| | Moderate nausea or vomiting | 2 |
| | Severe nausea and vomiting, incapacitating | 3 |
| Fatigue and/or weakness | Not tired or weak | 0 |
| | Mild fatigue/weakness | 1 |
| | Moderate fatigue/weakness | 2 |
| | Severe fatigue/weakness, incapacitating | 3 |
| Dizziness/light-headedness | No dizziness/light-headedness | 0 |
| | Mild dizziness/light-headedness | 1 |
| | Moderate dizziness/light-headedness | 2 |
| | Severe dizziness/light-headedness, incapacitating | 3 |
| Difficulty sleeping | Slept as well as usual | 0 |
| | Did not sleep as well as usual | 1 |
| | Woke many times, poor sleep | 2 |
| | Could not sleep at all | 3 |

A total score of 3 to 5 indicates mild AMS
A score of 6 or more signifies severe AMS

Sickness-Cerebral Score, Visual Analog Scale for the Overall Feeling of Mountain Sickness and Clinical Functional Score (CFS).

*Q6: How will you manage the case of HACE and HAPE?*

A:

1. ***Descent:*** Immediate descent at the first suspicion of HACE, while the patient is still ambulatory, is the gold standard treatment in those who develop HACE. A descent of approximately 1000 m is usually lifesaving [5]. Other treatment options should not delay descent, rather, it should be reserved for situations where descent is not possible or may be delayed [6].
2. ***Supplemental oxygen:*** Oxygen delivered by face mask or preferably non-rebreathing mask to maintain peripheral capillary oxygen saturation ($SpO_2$) > 90% is recommended [1]. It should however be noted that at high altitude $PAO_2$ is low and consequently $PaO_2$ and $SpO_2$ shows lower values that may be normal for that patient at that altitude.
3. ***Hyperbaric therapy:*** Portable hyperbaric chambers (such as the Gamow bag) should be used for patients with severe AMS or HACE when descent is delayed or not possible and supplemental oxygen is not available [1]. However, symptoms may recur when individuals are removed from the chamber, thus, use of a portable hyperbaric chamber should not delay descent in situations where descent is required such as in the case of HACE and HAPE.

4. ***Dexamethasone:*** Though studies are lacking supporting the use of dexamethasone for HACE, its use has been recommended based upon extensive clinical experience. The recommended initial dose is 8 to 10 mg orally, intramuscularly, or intravenously (IV), followed by 4 mg every six hours until symptoms resolve. The pediatric dose is 0.15 mg/kg/dose every 6 h [1]. The mechanism by which dexamethasone works is unclear, however, reduction in vascular permeability, inflammatory pathway inhibition, antioxidant balance, aquaporin-4 channel (AQP4) modulation and sympathetic blockade have all been proposed to help in the prevention and treatment of high-altitude cerebral edema [7].

## Evidence Contour

1. **Acetazolamide:** Acetazolamide has been shown to accelerate acclimatization to high altitude. Similarly multiple trials have established a role for acetazolamide in prevention of AMS [8–11]. However few studies have rigorously assessed the effectiveness of acetazolamide in the treatment (rather than prophylaxis) of AMS. A small study used acetazolamide for AMS and found it to be effective [12], however, the diuretic effect of acetazolamide might provoke hypotension in the intravascularly depleted patient, and the added stimulus to ventilation might worsen dyspnea. Hence, it is not recommended for the treatment for HACE and HAPE [1].
2. **Diuretics:** Many patients with AMS and HAPE have intravascular volume depletion and the use of diuretics in such patients may worsen the volume status further, hence diuretics should not be used for the treatment of HAPE [1].
3. **Nonsteroidal anti-inflammatory drugs and acetaminophen:** Acetaminophen, and ibuprofen has been found to relieve headache at high altitude but it is unclear whether they are useful as prophylaxis or treatment of AMS, HACE and HAPE [13, 14]. These drugs can be used to treat headache at high altitude but are not recommended for the prevention and treatment of HACE and HAPE [1].
4. **Nifedipine:** Extensive clinical experience and one randomized study has shown that Nifedipine in a dose of 30 mg of the extended-release preparation administered every 12 h is effective in preventing HAPE in susceptible people [15]. Similarly, though a single, nonrandomized, unblinded study found nifedipine useful for HAPE treatment when oxygen or descent was not available, another observational study of individuals with HAPE reported that nifedipine offered no advantage when used as an adjunct to oxygen and descent [16, 17]. Thus, nifedipine can be used for HAPE prevention in HAPE-susceptible people and as an adjunct to treatment when descent is impossible or delayed and reliable access to supplemental oxygen or portable hyperbaric therapy is unavailable [1].
5. **Phosphodiesterase inhibitors:** Tadalafil and sildenafil are phosphodiesterase-5 (PDE-5) inhibitors that augment the pulmonary vasodilatory effects of nitric oxide and thus cause pulmonary vasodilation and decrease pulmonary artery pressure. Though there is a strong physiologic rationale for using phosphodiesterase inhibitors in HAPE, supported by evidences for its use as prophylaxis for HAPE, however, no systematic study has examined the role of tadalafil or

sildenafil in HAPE treatment as either mono- or adjunctive therapy [18, 19]. Tadalafil and sildenafil can be used for HAPE prevention in known susceptible individuals who are not candidates for nifedipine as well as for the treatment of HAPE when descent is impossible or delayed, access to supplemental oxygen or portable hyperbaric therapy is impossible, and nifedipine is unavailable [1].

6. **Ginkgo biloba:** Ginkgo biloba is an herbal extract preparation with variable compositions. Though some small studies have suggested the effectiveness of ginkgo biloba at reducing the symptoms of AMS in adults, larger trials have failed to demonstrate the benefit [20–22]. Ginkgo biloba has not been recommended for AMS prevention and treatment [1].
7. **Beta agonist:** Barring few case reports of beta-agonist use in HAPE treatment [23], no data exists to support the use of beta agonists for HAPE, hence there is no recommendation in its use [1].

*Q7: What ventilatory strategy would you consider in such patients?*

**A: Role of Continuous positive airway pressure**

CPAP increases transmural pressure across alveolar walls which increases alveolar volume and thus leads to an improvement in ventilation-perfusion matching and gas exchange [1]. However, there are no controlled studies to show improvement in patient outcomes with the use of CPAP or EPAP compared to oxygen alone or in conjunction with medications in patients who have developed AMS or HAPE. Few reports have shown that CPAP can be used as an adjunct for treating HAPE [24, 25], and since the risks associated with the therapy is low, CPAP or EPAP can be considered an adjunct to oxygen administration, provided the patient has normal mental status and can tolerate the mask [1].

Since this patient has hypoxemia ($SpO_2$–77%) at our center, which is at a level higher than sea level, but not high enough to level $SpO_2$ of 77% as normal, a trial of CPAP can be given if his saturation cannot be maintained with nasal cannula/face mask/venturi mask. However, his GCS has to be monitored continuously and ABG repeated to monitor improvement in hypoxia. Once the hypoxemia improves and the patient becomes fully conscious, he can be taken off CPAP and kept in nasal cannula/face mask/venturi mask. However, if his GCS falls further or he cannot tolerate the mask, CPAP should be discontinued and consideration should be given for endotracheal intubation and mechanical ventilation.

## Role of Mechanical Ventilation

The management of patients with HACE who require mechanical ventilation can be challenging. Though intubation and short-term hyperventilation is a possible therapeutic option in patients with cerebral edema who have clinically significant ICP elevation, these patients are likely to have a respiratory alkalosis, and overventilation could cause cerebral ischemia. Oxygen alone markedly decreases cerebral blood flow and ICP at high altitude, thus providing high $FiO_2$ might be detrimental. The optimal PEEP and tidal volume are another controversial aspect in the

ventilatory management of such patients. In a recent survey by ESICM, most clinicians utilize a tidal volume of 6–8 ml/kg and low PEEP than suggested by ARDS Net in patients with severe traumatic brain injury [26].

Since there are no systematic studies regarding ventilatory settings in patients with HACE and HAPE, evidences and recommendations are lacking. A general approach would be to utilize lung protective ventilation with a target $PaO_2$ 80–120 mm Hg, target $PaCO_2$ 35–45 mm Hg, use the low PEEP/$FiO_2$ table of ARDS Net protocol and titrate the settings according to the response of the patient [27].

This patient had rapidly descended via heli-rescue and brought to our center. He was given oxygen via face-mask initially which improved his $SpO_2$ improved to 86%, however, his $SpO_2$ was not maintained in the target range, hence CPAP of 10 cm H2O was started which improved his $SpO_2$ to 94%. He was started on Inj Dexamethasone 4 mg iv every six hourly, tab nifedipine 30 mg ever 12 hourly and Inj paracetamol 1 gm iv every 6 hourly. His cognitive functions started improving within 6 h. On second day of admission, CPAP was stopped and he was put on face-mask. However, his ataxia improved slowly, and by the fourth day of hospitalization, his chest was clear and his gait was normal. Repeat chest radiograph on the fourth day of admission showed complete resolution of the opacities. A repeat NCCT-head performed on the fourth day also showed that the white matter edema had subsided with decreased mass effect and the grey–white matter differentiation was seen to be normal. He was discharged on the tenth day.

The following definitions on the diagnosis of altitude illness were adopted at the 1991 International Hypoxia Symposium, held at Lake Louise in Alberta, Canada [28].

| | |
|---|---|
| Acute Mountain sickness (AMS) | In the setting of a recent gain in altitude, the presence of headache and at least one of the following symptoms:<br>1. Gastrointestinal<br>2. Fatigue or weakness<br>3. Dizziness or lightheadedness<br>4. Difficulty sleeping |
| HIGH ALTITUDE CEREBRAL EDEMA (HACE) | Can be considered “end stage” or severe AMS.<br>In the setting of a recent gain in altitude, either:<br>1. The presence of a change in mental status and/or ataxia in a person with AMS<br>2. Or, the presence of both mental status changes and ataxia in a person without AMS |
| HIGH ALTITUDE PULMONARY EDEMA (HAPE) | In the setting of a recent gain in altitude, the presence of the following:<br>Symptoms: At least two of:<br>1. Dyspnea at rest<br>2. Cough<br>3. Weakness or decreased exercise performance<br>4. Chest tightness or congestion<br>Signs: At least two of:<br>1. Crackles or wheezing in at least one lung field<br>2. Central cyanosis<br>3. Tachypnea<br>4. Tachycardia |

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