MOUNTAIN SICKNESS - PATHOPHYSIOLOGICAL AND PHARMACOLOGICAL ASPECTS

Rima Shah*, Aditya Kadeval**, Darshil Shah***, Jignesh Shah****

*Associate professor, Department of Pharmacology, All India Institute of Medical Sciences (AIIMS, Rajkot),
** Junior Resident, Department of Pharmacology, All India Institute of Medical Sciences (AIIMS, Rajkot),
Assistant Professor, Department Of Quality assurance, L J institute of Pharmacy, L J university, Ahmedabad*Professor, Department Of Quality assurance, L J institute of Pharmacy, L J University, Ahmedabad

Abstract: High-altitude illness resulting due to hypoxia is a group of syndromes which leads to various physiological alterations in our body. Acute Mountain sickness (AMS) is the predominant and is commonly associated with headache, fatigue, shortness of breath, sleeplessness, and anorexia, which if untreated may progress to the life-threatening conditions of high-altitude pulmonary edema (HAPE) or high-altitude cerebral adenoma (HACE). HACE is much more likely in those HAPE. It is one of the most lethal high-altitude illnesses and has been reported in 0.1% of tourists and as many as 15.5% of climbers involved in a rapid ascent. HACE is a significant fatal condition which is associated with high altitude illness arising of late or end-stage acute AMS. HAPE is a non-cardiogenic pulmonary edema which is preceded by symptoms of acute mountain sickness commonly characterized by subtle non-productive cough, dyspnea on exertion. At higher altitudes cerebral edema leads to severe neurological dysfunction which was confirmed from autopsy results in previous studies. This article focusses on possible pathophysiological mechanisms, risk factors responsible for AMS, HACE and HAPE and its pharmacological considerations.

Key words: Acute mountain sickness (AMS), high altitude pulmonary edema (HAPE), High altitude cerebral edema (HACE), high altitude sickness

Running title: Mountain sickness

Corresponding Author: Dr. Rima Shah, Department of Pharmacology, All India Institute of Medical Sciences (AIIMS),Rajkot, Gujarat, Email: rima_1223@yahoo.co.in,Phone: 9825741010

Introduction

In recent years there has been tremendous increase in the interest of people in travelling to high altitudes due to growth of ecotourism and global adventure travel. At higher altitudes above 2500m there is a significant decrease in partial pressure of oxygen and barometric pressure. (1, 2)High-altitude illness (HAI) would take place in case of faster elevation to higher altitudes wherein the human body do not get sufficient time to adapt and acclimatize to hypobaric hypoxia. High-altitude illness resulting due to hypoxia is a group of syndromes which leads to various physiological alterations in our body. (1, 2)

High altitude illness mainly encompasses cerebral and pulmonary syndromes including acute mountain sickness and high-altitude cerebral edema referring to the cerebral abnormalities, and high-altitude pulmonary edema referring to the pulmonary abnormalities. (3, 4)Acute Mountainsickness (AMS) is a predominant and is commonly associated with headache, fatigue, shortness of breath, sleeplessness, and anorexia, which if untreated may progress to the life-threatening conditions of high-altitude pulmonary edema or high-altitude cerebral edema. (3, 4)

High altitude cerebral edema (HACE) is a significant fatal condition which is associated with high altitude illness arising of late or end-stage acute AMS. It is often characterized by ataxia, fatigue, and altered mental status. (5) HACE represents the least common form of altitude illness, however it is critical that it be rapidly diagnosed and managed, as it can progress to coma and death as a result of brain herniation within 24 hours. (5) High altitude pulmonary edema(HAPE) is a non-cardiogenic pulmonary edema which is preceded by symptoms of acute mountain sickness commonly characterized by subtle non-productive cough, dyspnea on exertion. (5) The cough may worsen and it may lead to a debilitating degree of dyspnoea, even at rest with common clinical features like cyanosis, tachypnea, tachycardia and elevated body temperature. (5)

This article focusses on possible pathophysiological mechanisms, risk factors responsible for AMS, HACE and HAPE and its pharmacological considerations for AMS, HACE

and HAPE. It also aims to elaborate various modalities for their prevention and treatment.

A) High-altitude cerebral edema (HACE)

a. Etiology, Epidemiology and risk factors of HACE

High-altitude cerebral edema is a potentially fatal neurological syndrome representing the end stage of acute mountain sickness. It is mysterious and rare malady brought about by exposure to the thin air of high altitude, developed secondary to acute mountain sickness or high-altitude pulmonary edema. (6, 7) HACE is mainly associated with headache, lassitude, insomnia, anorexia, nausea, ataxia of gait, altered consciousness, papilledema and brain edema. (8) HACE mainly is observed in unacclimatized persons at altitudes above 2000 m commonly with abrupt ascent to over 3000 m. Global Incidence of HACE is found to be 0.5-1% at higher altitudes of 4000-5000 m. (8) All ages and genders are affected with particularly younger males are at higher risk due to continuation of ascentdespite symptoms of AMS and faster rate of ascent. (9) Previous history of high-altitude illness with lack of acclimatization and heavy physical exertion were common risk factors of HACE. HACE is much more likely in those with high altitude pulmonary edema. (9) Gabry et al. (2003) found that 13% of 52 patients with HAPE in the French Alps had stupor or coma. Hultgren et al. (1996) reported that 14% of 150 patients with HAPE in the Colorado Rockies had HACE, and 20% of 50 HAPE patients evacuated by helicopter in the Swiss Alps also had HACE. (9)

b. Clinical presentation and diagnosis of HACE

Drowsiness and subtle psychological changes are the first presenting symptoms among patients with HACE accompanied with withdrawal and apathetic condition. Anorexia and nausea with auditory and visual hallucinations are commonly observed symptoms. (10 - 12) Coma, retinal haemorrhages and hyponatremia are uncommon and critical findings among most seriously ill patients. Occurrence of small petechial haemorrhages and venous sinus thromboses are the end stage findings. (10 - 12)Careful fundoscopy can reveal progression of retinal pathology at altitude is an indication of impending HACE. CT scan images often demonstrates compression of sulci and flattening of gyri. (10 - 12) HACE are commonly associated with elevated CSF pressures more than 200 mmH2O that can be determined through Lumbar punctures. Earlier diagnostic research has revealed formation of edema in the white matter corpus callosum without involvement of grey matter indicating the edema of vasogenic origin. (10 - 12)

c. Pharmacology of HACE

At higher altitudes cerebral edema leads to severe neurological dysfunction which was confirmed from autopsy results in previous studies. HACE is a considered to be a critical vasogenic edema which causes disruption of blood–brain barrier. (13 - 15) This is a result of cerebral capillary hypertension which is associated with increased white matter T2 signal causing impaired cerebral autoregulation. In cases of hypoxia induced cerebral vasodilatation impairment of cerebral venous return takes place which results in cerebral capillary hypertension. (13 - 15) Various Chemical mediators of permeability including bradykinin, histamine, arachidonic acid, oxygen and hydroxyl free radicals, and iNOS-generated nitric oxide could cause vasogenic edema. In cases of elevated cerebral capillary pressure even a minor leakage of chemical mediators can lead to brain edema. (13 - 15) Earlier studies have reported that vascular endothelial growth factor increases vascular permeability leading to vasogenic edema which plays an important role in development of HACE. (13 - 15)

d. Treatment and Clinical Course of HACE

Apparently, there is no correlation between the degree of cerebral edema and severity of clinical presentation and outcome. The symptoms depend upon astrocytic swelling caused by redistribution of fluid in the intracellular space. (16, 17) Rapid descent is the gold standard treatment in those who develop HACE which should be done immediately by 300 to 1000 m and continued till patient is asymptomatic. Supplemental oxygen with 90% saturation should be given in severe case with careful management of prolonged hyperoxia. (16, 17) Intravenous administration of dexamethasone with a loading dose of 8mg followed by 4mg dose every 6 hours helps in ameliorating vasogenic edema by stabilizing blood brain barrier and attenuating anti-inflammatory responses. (16, 17)Rapid airway management and bladder drainage are performed to reduce intracranial pressure in patients in coma

condition. Earlier studies have reported use of loop diuretics including furosemide 40 to 80 mg or bumetanide 1 to 2 mg to reduce brain hydration. (16, 17)

B) High-altitude pulmonary edema (HAPE)

a. Etiology, Epidemiology and risk factors of HAPE

High-altitude pulmonary edemais a potentially life-threatening condition which typically occurs in young, otherwise healthy people after rapid ascent to an altitude of 2500m or higher. (18, 19) It is one of the most lethal high-altitude illnesses and has been reported in 0.1% of tourists and as many as 15.5% of climbers involved in a rapid ascent. HAPE is also seen in approximately 5%–10% of climbers with AMS. (18, 19) Commonly associated risk factors include individual susceptibility to low hypoxic ventilatory response (HVR), higher altitude attained, a rapid rate of ascent, male sex, use of sleep medication, excessive salt ingestion, ambient cold temperature, and heavy physical exertion. (20)Pre-existing conditions such as those leading to increased pulmonary blood flow, pulmonary hypertension, increased pulmonary vascular reactivity, or patent foramen ovale have a higher predisposition towards the development of HAPE. (20) The incidence is 0.6% to 6% at 4500 mt, and the incidence is 2% to 15% at 5500mt, with higher incidence associated with faster ascent time. The rate of mortality is about 11% in treated patients and about 50% in untreated patients. (21, 22)

b. Clinical presentation and diagnosis of HAPE

Dry cough, chest tightness, decreased exercise tolerance, and dyspnea at rest are common initial symptoms of HAPE. Patients with dyspnea associated with cough at rest are exposed at the onset of HAPE which induces an inflammatory response in the lungs. (23, 24) On clinical examination tachypnea, tachycardia, crackles, and a relative cyanosis or decreased oxygen saturation is observed. With the progress of HAPE dyspnea at rest worsens. The cough becomes frothy and significantly increases and later blood can be found in the cough. (23, 24) As lungs auscultates further, wheezing and rales can be observed in patients which on further progress the patient would become more hypoxic and cyanotic which may cause mental stress, anxiety obtundation and even coma. (23, 24)

Chest X-ray indicated patchy unilateral or bilateral fluffy infiltrates and a normal cardiac silhouette. Bronchoalveolar lavage examination indicated increased cellularity and the presence of chemotactic (leukotriene B4) and vasoactive (thromboxane B2) mediators andlavage fluid also demonstrated high protein and red blood cell content. (25 - 27) These results were also compared and correlated with the pulmonary artery pressures measure by echocardiography and as there were no positive reports of cytokine expression or neutrophil presence it confirmed the notion that the actual course of HAPE development is through high intravascular pressure and not inflammatory process. (25 - 27)

c. Pharmacology of HAPE

HAPE is a form of noncardiogenic pulmonary edema wherein pulmonary artery pressures play a dominant role in its development and progress. Hypoxic condition causes hypoxic pulmonary vasoconstriction (HPV) which cause elevated pressure and flow in the perfused areas, resulting in pulmonary hypertension and subsequent edema. (28) It is also evident that increased sympathetic tone and alterations in vasoactive mediators (endothelin [ET-1], nitric oxide [NO]) produced by pulmonary endothelial cells also leads to HPV.In HAPE-susceptible individuals, the levels of endothelial derived pulmonary vasoconstrictor ET-1 gets elevated while the levels of NO reduce in HAPE. (29, 30) At higher altitudes the levels of NO decreases with simultaneous increase in free radicals in pulmonary circulation causes imbalance of vasoconstrictors (ET-1) and vasodilators (NO) which constitutes an important predisposing factor in HAPE. This vasoconstriction causes non-inflammatory leakage of fluid across the alveolar-capillary membrane which is later followed by a secondary inflammatory reaction. (29, 30)

d. Treatment and Clinical Course of HAPE

HAPE being the life-threatening condition, an immediate arrest to the progression of disease is required through improvement in oxygenation. An immediate initiation of high-flow supplemental oxygen at rest and sitting in an upright position should be performed. (31 - 33)Subsequent improvement in oxygen level within first few

hours' maintenance of oxygenation (oxygen saturation >90%) with low-flow supplemental oxygen and rest is often required for 2–3 days. Pharmacological treatment is based upon agents that reduce pulmonary artery pressure which in turn improves oxygenation in HAPE. (31 - 33) Nifedipine, nitric oxide, epoprostenol, and sildenafil are extensively studied drugs for their use in treatment of HAPE. β-agonists drugs can cause increase the clearance of fluid from the alveolar space which might lower pulmonary artery pressure. (31 - 33)

Conclusion

At higher altitudes above 2500m there is a significant decrease in partial pressure of oxygen and barometric pressure. High-altitude illness resulting due to hypoxia is a group of syndromes due to alteration in the physiology. It mainly encompasses cerebral and pulmonary syndromes including acute mountain sickness and high-altitude cerebral edema referring to the cerebral abnormalities, and high-altitude pulmonary edema referring to the pulmonary abnormalities. HACE is mainly associated with headache, lassitude, insomnia, anorexia, nausea, ataxia of gait, altered consciousness, papilledema and brain edema. Drowsiness and subtle psychological changes are the first presenting symptoms among patients with HACE accompanied with withdrawal and apathetic condition with raised intracranial tension. Rapid descent and intravenous dexamethasone are standard treatment for it. HAPE is usually presents with cough and dyspnoea with high intravascular pressure and can be treated effectively with oxygen therapy.

References:

1. Bhagi S, Srivastava S, Singh SB. High-altitude pulmonary edema: review. J Occup Health. 2014;56(4):235-43. doi: 10.1539/joh.13-0256-ra. PMID: 24872194.
2. Bärtsch P, Mairbäurl H, Swenson ER, Maggiorini M. High altitude pulmonary oedema. Swiss Med Wkly. 2003 Jul 12;133(27-28):377-84. doi: 10.4414/smw.2003.09657. PMID: 12947525.
3. Korzeniewski, K., 2014. High mountain conditions. In: Korzeniewski, K. (Ed.), Travel Medicine. Military Institute of Medicine, Department of Epidemiology and Tropical Medicine, Warszawa, Poland, pp. 284–291 (in Polish).
4. Korzeniewski K. Zagrozenia środowiskowe w rejonie operacji wojskowych w Iraku i Afganistanie [Environmental risk factors in the territory of military operations in Iraq and Afghanistan]. Pol Merkur Lekarski. 2008 Jul;25(145):5-8. Polish. PMID: 18839605.
5. Lobenhoffer, H.P., Sink, R.A., Brendel, W., 1982. High altitude pulmonary edema: analysis of 166 cases. In: Brendel, W., Zink, R.A. (Eds.), High Altitude Physiology and Medicine. Springer-Verlag, New York, NY, pp. 219–231
6. Gonzalez Garay A, Molano Franco D, Nieto Estrada VH, Martí-Carvajal AJ, Arevalo-Rodriguez I. Interventions for preventing high altitude illness: Part 2. Less commonly-used drugs. Cochrane Database Syst Rev. 2018 Mar 12;3(3):CD012983. doi: 10.1002/14651858.CD012983. PMID: 29529715; PMCID: PMC6494375.
7. Nieto Estrada VH, Molano Franco D, Medina RD, Gonzalez Garay AG, Martí-Carvajal AJ, Arevalo-Rodriguez I. Interventions for preventing high altitude illness: Part 1. Commonly-used classes of drugs. Cochrane Database Syst Rev. 2017 Jun 27;6(6):CD009761. doi: 10.1002/14651858.CD009761.pub2. PMID: 28653390; PMCID: PMC6481751.
8. Clarke C. High altitude cerebral oedema. Int J Sports Med. 1988 Apr;9(2):170-4. doi: 10.1055/s-2007-1024999. PMID: 3384523.
9. Dickinson, J.G. (1983). High altitude cerebral edema: Cerebral acute mountain sickness. Semin. Respir. Med. 5:151–158.
10. Dong Q, Welsh RC, Chenevert TL, Carlos RC, Maly-Sundgren P, Gomez-Hassan DM, Mukherji SK. Clinical applications of diffusion tensor imaging. J Magn Reson Imaging. 2004 Jan;19(1):6-18. doi: 10.1002/jmri.10424. PMID: 14696215.
11. Hackett PH. High altitude cerebral edema and acute mountain sickness. A pathophysiology update. Adv Exp Med Biol. 1999;474:23-45. doi: 10.1007/978-1-4615-4711-2_2. PMID: 10634991.
12. Hackett PH, Yarnell PR, Hill R, Reynard K, Heit J, McCormick J. High-altitude cerebral edema evaluated with magnetic resonance imaging:

clinical correlation and pathophysiology. JAMA. 1998 Dec 9;280(22):1920-5. doi: 10.1001/jama.280.22.1920. PMID: 9851477.
13. Hackett PH, Roach RC. High altitude medicine. In: Auerbach PS, editor. *Wilderness medicine.* 5th ed. Philadelphia: Mosby Elsevier; 2007. Available from: www.mdconsult.com/book/body/176973547-2/0/1483 [accessed on 2023 Jan 1]
14. Hackett PH, Roach RC, Wood RA, Foutch RG, Meehan RT, Rennie D, Mills WJ Jr. Dexamethasone for prevention and treatment of acute mountain sickness. Aviat Space Environ Med. 1988 Oct;59(10):950-4. PMID: 3190622.
15. Oelz O. High altitude cerebral oedema after positive airway pressure breathing at high altitude. Lancet. 1983 Nov 12;2(8359):1148. doi: 10.1016/s0140-6736(83)90666-9. PMID: 6138679.
16. Pardridge WM. Molecular biology of the blood-brain barrier. Methods Mol Med. 2003;89:385-99. doi: 10.1385/1-59259-419-0:385. PMID: 12958435.
17. Johnson TS, Rock PB, Fulco CS, Trad LA, Spark RF, Maher JT. Prevention of acute mountain sickness by dexamethasone. N Engl J Med. 1984 Mar 15;310(11):683-6. doi: 10.1056/NEJM198403153101103. PMID: 6700643.
18. Houston CS. Acute pulmonary edema of high altitude. N Engl J Med. 1960 Sep 8;263:478-80. doi: 10.1056/NEJM196009082631003. PMID: 14403413.
19. Auerbach PS. Wilderness Medicine. 5th ed. Philadelphia: Mosby Elsevier; 2007.
20. Hultgren H, Spickard W. Medical experiences in Peru. 1960. Wilderness Environ Med. 1998 Fall;9(3):166-85; discussion 186-7. doi: 10.1580/1080-6032(1998)009[0166:meip]2.3.co;2. PMID: 11990188.
21. Bärtsch P, Maggiorini M, Ritter M, Noti C, Vock P, Oelz O. Prevention of high-altitude pulmonary edema by nifedipine. N Engl J Med. 1991 Oct 31;325(18):1284-9. doi: 10.1056/NEJM199110313251805. PMID: 1922223.
22. Smith CA, Dempsey JA, Hornbein TF: Control of breathing at high altitude. In Hornbein TF, Schoene RB, editors: High altitude: an exploration of human adaptation, New York, 2001, Marcel Dekker, pp 139–174.
23. Monge MC: La enfermedad de los Andes: sindromes eritremicos. Ann Fac Med Univ San Marcos (Lima) 11:1–316, 1928.
24. Winslow RM: Relationship between erythropoiesis and ventilation in high altitude natives. In Lahiri S, Cherniack NS, Fitzerland RS, editors: Response and adaptation to hypoxia: organ to organelle, New York, NY, 1991, Oxford University Press, pp 143–156.
25. Scherrer U, Rexhaj E, Jayet PY, Allemann Y, Sartori C. New insights in the pathogenesis of high-altitude pulmonary edema. Prog Cardiovasc Dis. 2010 May-Jun;52(6):485-92. doi: 10.1016/j.pcad.2010.02.004. PMID: 20417341.
26. Shoene RB, Swenson ER. High-altitude pulmonary edema. In: Swenson ER, Bartsch P, editors. High altitude: human adaptation to hypoxia. New York: Springer; 2014, pp. 405–427.
27. Brugger H, Pun M, Swenson ER, Falk M. Research in High-Altitude and Mountain Emergency Medicine: Is Methodology Key? High Alt Med Biol. 2018 Mar;19(1):1-3. doi: 10.1089/ham.2017.0124. Epub 2017 Nov 13. PMID: 29131669; PMCID: PMC5905851.
28. Schaible B, Schaffer K, Taylor CT. Hypoxia, innate immunity and infection in the lung. Respir Physiol Neurobiol. 2010 Dec 31;174(3):235-43. doi: 10.1016/j.resp.2010.08.006. Epub 2010 Aug 13. PMID: 20709192.
29. Oelz O, Maggiorini M, Ritter M, Waber U, Jenni R, Vock P, Bärtsch P. Nifedipine for high altitude pulmonary oedema. Lancet. 1989 Nov 25;2(8674):1241-4. doi: 10.1016/s0140-6736(89)91851-5. PMID: 2573760.
30. Luks AM. Physiology in Medicine: A physiologic approach to prevention and treatment of acute high-altitude illnesses. J Appl Physiol (1985). 2015 Mar 1;118(5):509-19. doi: 10.1152/japplphysiol.00955.2014. Epub 2014 Dec 24. PMID: 25539941.
31. Beall CM, Laskowski D, Strohl KP, Soria R, Villena M, Vargas E, Alarcon AM, Gonzales C, Erzurum SC. Pulmonary nitric oxide in mountain dwellers. Nature. 2001 Nov 22;414(6862):411-2. doi: 10.1038/35106641. PMID: 11719794.

32. Maggiorini M, Brunner-La Rocca HP, Peth S, Fischler M, Böhm T, Bernheim A, Kiencke S, Bloch KE, Dehnert C, Naeije R, Lehmann T, Bärtsch P, Mairbäurl H. Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema: a randomized trial. Ann Intern Med. 2006 Oct 3;145(7):497-506. doi: 10.7326/0003-4819-145-7-200610030-00007. PMID: 17015867.
33. West JB, Tsukimoto K, Mathieu-Costello O, Prediletto R. Stress failure in pulmonary capillaries. J Appl Physiol (1985). 1991 Apr;70(4):1731-42. doi: 10.1152/jappl.1991.70.4.1731. PMID: 2055852.