HIGH-ALTITUDE CEREBRAL OEDEMA (HACE): A HEALTH CHALLENGE IN EXTREME ENVIRONMENTS

Wysokościowy obrzęk mózgu (HACE): wyzwanie zdrowotne w ekstremalnych warunkach środowiskowych

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Abstract

High-altitude cerebral oedema is one of the three forms of altitude sickness and is considered one of its most serious complications. Its incidence is relatively low, but its rapid progression and worsening symptoms make it a life-threatening condition that requires immediate medical attention. The growing popularity of high-altitude tourism means that knowledge about altitude sickness and high-altitude cerebral oedema should be promoted not only among medical professionals but also among ordinary tourists planning high-mountain expeditions. The following paper, which is a narrative review describing high-altitude cerebral oedema, discusses the key pathogenetic elements of this condition, including molecular mechanisms resulting from exposure to hypobaric hypoxia, blood-brain barrier dysfunction, increased vascular permeability, and the development of both vasogenic and cytotoxic oedema. Epidemiological data and risk factors are presented, followed by the spectrum of clinical manifestations, ranging from non-specific, mild symptoms that may coexist with an episode of acute mountain sickness to ataxia, impaired consciousness, and other severe neurological signs. The paper addresses diagnostic issues, with particular emphasis on the usefulness of imaging tests, specifically magnetic resonance imaging, in the process of confirming the diagnosis. Finally, the role of rapid implementation of appropriate therapy, consistent with current medical knowledge and consisting of altitude reduction, oxygen therapy, administration of steroids, and, in difficult conditions, the use of a portable hyperbaric chamber, is emphasised. High-altitude cerebral oedema remains a challenge that should always be managed by an interdisciplinary team; however, further research is needed to deepen our understanding of the pathophysiology, diagnosis, and treatment of this condition.

Streszczenie

Wysokościowy obrzęk mózgu stanowi jedną z trzech form choroby wysokościowej i jest uważany za jedno z jej najpoważniejszych powikłań. Częstość jego występowania jest stosunkowo niska, ale szybka progresja i narastanie objawów sprawiają, że jest to stan zagrażający życiu, wymagający natychmiastowej pomocy medycznej. Ze względu na rosnącą popularność turystyki wysokogórskiej, wiedza na temat choroby wysokościowej i wysokościowego obrzęku mózgu powinna być propagowana zarówno wśród osób związanych z medycyną, jak i wśród turystów planujących wysokogórskie ekspedycje. W niniejszym przeglądzie narracyjnym omówiono kluczowe elementy patogenezy wysokościowego obrzęku mózgu, w tym mechanizmy molekularne wynikające z przebywania w warunkach hipoksji hipobarycznej, dysfunkcji bariery krew–mózg, zwiększonej przepuszczalności naczyń krwionośnych oraz powstawania obrzęku naczyniowego i cytotoksycznego. Przedstawiono dane epidemiologiczne wraz z czynnikami ryzyka, a następnie spektrum objawów klinicznych, od niespecyficznych, łagodnych, które mogą współistnieć z epizodem ostrej choroby wysokogórskiej, po ataksję, zaburzenia świadomości i inne ciężkie objawy neurologiczne. Omówiono również zagadnienia diagnostyczne, ze szczególnym uwzględnieniem przydatności badań obrazowych, zwłaszcza rezonansu magnetycznego, w procesie potwierdzania rozpoznania. Na koniec podkreślono rolę szybkiego wdrożenia odpowiedniej terapii, zgodnej z aktualną wiedzą medyczną i obejmującej obniżenie wysokości, tlenoterapię, podawanie glikokortykosteroidów, a w trudnych warunkach – zastosowanie przenośnej komory hiperbarycznej. Wysokościowy obrzęk mózgu pozostaje istotnym wyzwaniem kliniczym, którym zawsze powinien zajmować się zespół interdyscyplinarny, ale do lepszego poznania jego patofizjologii, diagnostyki i leczenia konieczne są dalsze badania nad tajemnicami, które skrywa przed nami ta jednostka chorobowa.

Keywords: hypobaric hypoxia; acclimatisation; blood–brain barrier; high-altitude cerebral oedema; HACE

Słowa kluczowe: hipoksja hipobaryczna; aklimatyzacja; bariera krew–mózg; wysokościowy obrzęk mózgu; HACE

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Introduction

For hundreds of years, mountains have been a fascinating and intriguing object of human endeavour. These beautiful, expansive landscapes offer space for recreation, rest, and the restoration of well-being. With technological advances, they are becoming increasingly accessible, and what was once the domain of pioneers who made headlines after each expedition is now completely different. For many tourists, crossing the barrier of 4,000 or 5,000 metres above sea level is no longer an extraordinary challenge. This fact should inspire humility towards the mountains, given the physiological consequences they may impose. We must remember that the breathtaking views from high peaks can, under conditions of hypobaric hypoxia, pose a serious and sometimes even fatal threat.

The most common form of altitude illness, typically associated with milder symptoms, is acute mountain sickness (AMS). This syndrome occurs in climbers at altitudes above 2,500 metres above sea level, especially those who ascend too quickly and without proper acclimatisation [1]. Symptoms develop within 6–12 hours and, according to the literature, most commonly include headaches (70–80% of patients), nausea, vomiting (30–50%), insomnia (30–50%), dizziness (50–60%), fatigue (40–60%), and loss of appetite (20–40%) [2]. In the vast majority of cases, mild symptoms resolve spontaneously with acclimatisation or descent. However, if symptoms are ignored and climbing is continued, severe organ complications may develop, including the other two forms of high-altitude sickness: high-altitude pulmonary oedema (HAPE) and high-altitude cerebral oedema (HACE) [3].

This work is a narrative review based on current scientific publications indexed in the PubMed, Scopus, and Web of Science databases. The study includes sources of varying scientific credibility – primarily current guidelines and expert consensus, followed by larger case series, and finally review papers on the pathogenesis, diagnosis and treatment of HACE.

Epidemiology and risk factors

As noted in the introduction, HACE is one of the most dangerous and potentially fatal complications of exposure to a low partial pressure of oxygen. Researchers estimate that the incidence of HACE among individuals travelling above 4,000 metres above sea level ranges from 0.5 to 1% [4]. It should be emphasised that a definitive epidemiological estimate is extremely difficult to obtain, and the literature reports a wide range of values. Studies indicate that differences in incidence may be related to genetic adaptation to hypoxia and more efficient oxygen transport mechanisms [5]. In addition to distinguishing between permanent high-altitude residents and visiting climbers, it is necessary to consider risk factors that help estimate the probability of developing HACE.

Risk factors:

- Climbing speed and acclimatisation – the literature cites fast climbing speed and lack of adequate acclimatisation time as the main risk factors for HACE [6, 7].
- Age and gender – researchers do not list these factors as significant, although some studies indicate that younger men, who may be more likely to ignore early warning signs, i.e., the initial symptoms of AMS, could have a higher incidence of HACE [8].
- Co-existence of HAPE – data show that up to 50% of patients who develop high-altitude pulmonary oedema also develop HACE [6].
- Cardiovascular, respiratory, and neurological diseases – conditions such as congenital heart defects, upper respiratory tract infections, and Parkinson's disease, have been identified as risk factors [9, 10].
- Chronic fatigue and significant exertion at high altitudes – these may contribute to the development of HACE [11].
- Migraine – the occurrence of migraines has been identified in the literature as a risk factor for altitude sickness and, indirectly, for HACE [12].

In light of these findings, HACE remains one of the rarest complications within the spectrum of altitude sickness from an epidemiological point of view, although this fact should not lead to underestimation of the risks associated with the development of this disease.

Notably, HACE does not occur during aircraft cabin depressurisation, as such events involve only short-term hypoxia, even if the equivalent altitude may transiently reach 4,000–7,000 metres. The brief duration of exposure is insufficient to disrupt the blood–brain barrier or trigger the vasogenic cerebral oedema characteristic of HACE. Instead, any neurological disturbances that may appear are more likely related to hypocapnic cerebral vasoconstriction or decompression sickness rather than to high-altitude cerebral oedema [13, 14]. Therefore, the next part of the article addresses the pathogenesis, symptoms, diagnosis, and treatment of HACE.

Pathogenesis

Before discussing the molecular and morphological changes that lead to HACE, it is necessary to understand how oxygen conditions change with increasing altitude:

- 1,500–3,500 metres above sea level – a slight decrease in oxygen saturation (SaO_2) and a decrease in partial oxygen pressure (PaO_2) to approximately 55–75 mmHg.
- 3,500–5,500 metres above sea level – a further decrease in SaO_2 to 75% and a decrease in PaO_2 to 40–60 mmHg.
- 5,500–8,850 metres above sea level – extreme altitudes, with the "death zone" above 8,000 metres. Saturation then drops to as low as 58%, and PaO_2 can fall to about 30 mmHg [15].

These values demonstrate how profoundly the conditions at high altitudes differ from those known from everyday life – at an altitude at or near sea level. High altitude exposes the human body to conditions of hypobaric hypoxia, which in turn, through damage to the blood–brain barrier, vasogenic and cytotoxic oedema, forms the basis for the development of HACE.

Thanks to experimental research conducted in recent years, including studies using animal models, several facts regarding the pathogenesis of HACE have been established:

- Hypoxic hypoxia induces the formation of Caveolin-1 in the endothelium of cerebral vessels, regulated by nuclear respiratory factor-1. This process promotes degradation of proteins such as Claudin-5, which damages endothelial junctions and increases the permeability of the blood–brain barrier [16, 17].
- Hypoxia activates HIF-1α pathways, which affects the synthesis of vascular endothelial growth factor (VEGF). VEGF increases vascular permeability by interfering with the distribution and expression of proteins that form tight junctions, such as occludin and Claudin-5. VEGF may also stimulate the synthesis of metalloproteinases, which further exacerbates damage to the blood–brain barrier [16, 18, 19].
- Blood–brain barrier damage may also result from increased expression of pro-inflammatory cytokines such as TNF-α and IL-1β. By acting through pathways such as MAPK, p38, and NF-κB, these cytokines reorganise intercellular junctions, increasing barrier permeability [4, 13, 20].
- Under conditions of hypoxia, free radicals are formed, which, as studies have shown, damage Na+/K+ ATPase ion pumps. Water and sodium accumulate intracellularly, causing oedema of neurons and astrocytes, followed by cytotoxic oedema, accompanying vasogenic oedema and deepening brain damage [4, 21, 22].
- Individual factors such as skull anatomy, subarachnoid space capacity, compensatory abilities of the circulatory and nervous systems, and adaptation to hypoxic conditions may influence how quickly and to what degree the above mechanisms cause clinically significant brain oedema [16, 21, 23, 24] (Fig. 1).

All the complexities of the processes described above contribute to a cascade of events which, if not interrupted, cause rapid deterioration of the patient's condition, putting them in a life-threatening situation. Despite clear progress in understanding what HACE actually is, many pieces of the puzzle remain unknown, which only emphasises the need for further clinical and experimental research.

Symptoms

Due to its clinical presentation, HACE is a rather heterogeneous set of symptoms that usually develop within 24–48 hours after reaching an altitude of over 4,000 meters above sea level [4].

The first phase consists of symptoms that can be classified as AMS, namely nausea, headache, dizziness, and general weakness. According to the Lake Louise criteria, AMS is diagnosed when the total score reaches three or more points, including at least one point for headache, following recent ascent to high altitude [1, 25] (Tab. 1).

An important moment in the evolution of the disease, when the differential diagnosis should shift towards HACE, is the onset of neurological symptoms. These may manifest gradually or progress rapidly, leading to a life-threatening condition. This is often described as encephalopathy, including ataxia and mental status changes such as increasing somnolence and confusion [1, 26].

Knowledge of the course of this clinical phase should immediately prompt the climber to stop ascending and begin descent, as the further presentation of the disease may become dramatic. Some patients experience loss of consciousness, coma, and seizures [27]. Noteworthy here is the case of a 23-year-old climber who developed a seizure and coma the day after experiencing mild symptoms of AMS. This case also demonstrates the potential reversibility of HACE: with appropriate diagnosis, including MR imaging and hyperbaric treatment, the man regained mobility and the seizures did not return [28].

Table 1. The Lake Louise Acute Mountain Sickness Score

Headache	0 – None 1 – Mild 2 – Moderate 3 – Severe, incapacitating
Gastrointestinal symptoms	0 – No symptoms 1 – Poor appetite/nausea 2 – Moderate nausea/vomiting 3 – Severe nausea/vomiting, incapacitating
Fatigue and/or weakness	0 – Not tired or weak 1 – Mild fatigue/weakness 2 – Moderate fatigue/weakness 3 – Severe fatigue/weakness, incapacitating
Dizziness/ light-headedness	0 – No symptoms 1 – Mild dizziness 2 – Moderate dizziness 3 – Severe dizziness, incapacitating
Stage of the disease: **1. Mild** AMS: 3 to 5 points **2. Moderate** AMS: 6 to 9 points **3. Severe** AMS: 10 to 12 points AMS – acute mountain sickness	

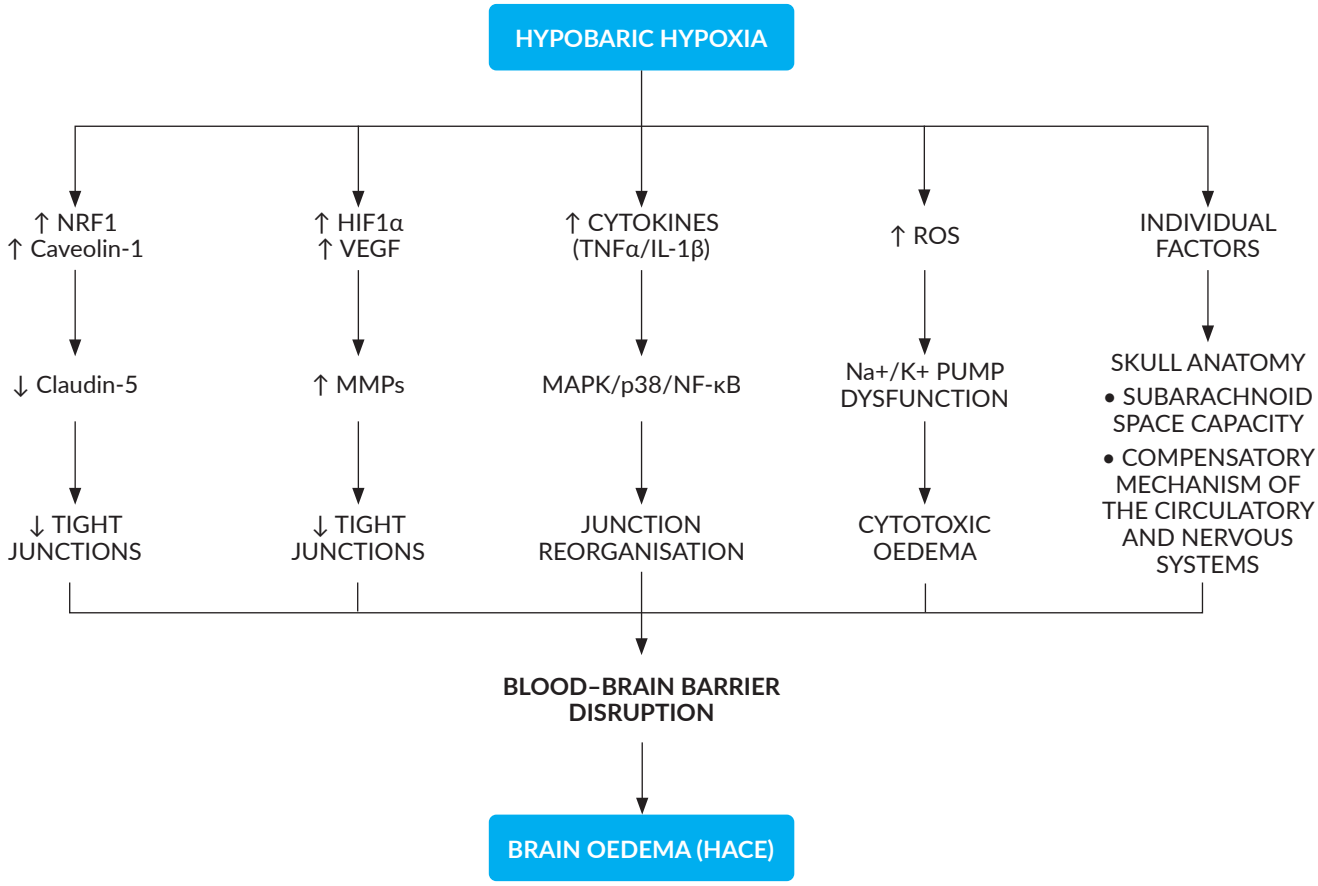

Figure 1. Pathogenesis of high-altitude cerebral oedema (HACE). NRF1 – nuclear respiratory factor 1; VEGF – vascular endothelial growth factor; NF-κB – nuclear factor kappa B; MAPK – mitogen-activated protein kinases; IL-1β – interleukin 1β; TNF-α – tumour necrosis factor α

Descriptions in the literature also include patients presenting symptoms atypical for HACE, such as the case of a 62-year-old patient who, while climbing and ascending to an altitude of about 3,500 metres above sea level, developed hiccups followed by slurred speech, headache, and nausea. After being transported to hospital, HACE was confirmed [29].

Other reviews have described symptoms such as diplopia, which, as shown during examination, was due to paralysis of cranial nerve VI (abducens nerve) and transient paresis of the left upper and lower limbs. The common denominator in both cases was the resolution of symptoms after descent to a lower altitude [30] (Tab. 2).

Diagnostics

The diagnostic process for high-altitude cerebral oedema is based on three pillars: the patient's clinical presentation, a well-collected medical history, and imaging tests (MRI/CT). The aim is to determine whether the presentation is truly consistent with HACE or with another disease producing similar symptoms. The literature states that the following conditions should be considered in the differential diagnosis:

- hypoglycaemia
- hypothermia
- hyponatraemia
- drug/alcohol intoxication
- carbon monoxide poisoning
- ketoacidosis
- cerebrovascular diseases: haemorrhage, stenosis
- meningitis
- epilepsy
- psychosis
- central nervous system tumours [4, 21].

Table 2. Symptoms of high altitude cerebral oedema (HACE) depending on disease phase

Phase of the disease	Symptoms
Prodromal phase/ co-occurrence of acute mountain sickness	• Nausea • Vomiting • Headache • Dizziness • Weakness/fatigue
Early HACE	• Ataxia • Somnolence • Confusion • Behavioural changes
Late HACE	• Loss of consciousness • Seizures • Coma
Atypical symptoms	• Diplopia – VI cranial nerve palsy • Hiccups • Slurred speech • Transient hemiplegia

Table 3. Findings observed depending on the selected imaging method

Head CT without contrast	• Diffuse cerebral oedema • Decreased density of white matter, especially in the corpus callosum region • Compression of the lateral and third ventricles • Blurring of sulci [26, 33]
Magnetic resonance imaging of the head	• Hypointense signal in the T1 sequence • Hyperintense signal in the T2 sequence • Hyperintense signal in the FLAIR and DWI sequences involving the corpus callosum, particularly the splenium, corona radiata, centrum semiovale, and parts of the internal capsule • SWI sequence may reveal microhaemorrhages, most often located in the corpus callosum and subcortically • Decreased ADC value • Indirect signs: narrowing, atrophy of the cerebral ventricles [26, 33–36]

While still in the field, diagnostic possibilities are limited, so attention should be focused on a thorough medical history, which includes questions about the pace and maximum altitude of ascent, chronic diseases, medications or stimulants used, previous episodes of altitude sickness, and the timing and sequence of symptoms [31]. Researchers also note that simple neurological tests assessing coordination or ataxia are extremely useful for evaluating AMS or HACE in mountain conditions: the straight-line walk test [27], the heel–knee test, and the finger–nose test [11].

After hospital admission, specific laboratory tests are performed, although in HACE the most important investigations are imaging tests. So far, no specific laboratory markers for high-altitude cerebral oedema have been identified. Some specialists cite leukocytosis as the only notable change in the patient's results, but this remains controversial, as such an increase may have completely different causes than cerebral oedema itself [4]. Laboratory tests are performed to rule out other causes of the patient's condition and include blood glucose levels, electrolytes, toxicology tests, and blood gas analysis [4, 6, 32]. Magnetic resonance imaging or computed tomography plays a significant role in diagnosis. CT is considered less valuable due to its reduced sensitivity in detecting mild forms of HACE, which may result in diagnostic errors [3, 26] (Tab. 3).

Treatment

The next step in managing HACE is the rapid initiation of treatment, the first stage of which is descending to a lower altitude, which will reduce hypoxia and stop the progression of cerebral oedema. During descent, physical exertion should be minimised as far as possible, as it may worsen the patient's prognosis [37, 38]. If immediate evacuation is not possible, guidelines and studies indicate the need for oxygen therapy (maintaining saturation at >90%) and consideration of a portable hyperbaric chamber (Gamow bag), which simulates descent to a lower altitude. These methods are effective, but not as effective as full evacuation [39, 40].

Another crucial aspect of treatment is the administration of glucocorticosteroids, specifically dexamethasone. Studies have shown that adult patients should be given an initial dose of 8 mg of dexamethasone, followed by 4 mg every 6 hours, administered orally, intravenously, or intramuscularly, depending on the patient's condition and capabilities. The steroid dosage for paediatric patients is 0.15 mg/kg of body weight every 6 hours. The molecular mechanisms of dexamethasone, based on cell membrane stabilisation, inhibition of angiogenesis, and modulation of nitric oxide synthase production, help reduce endothelial damage resulting from hypoxia [4, 15].

Acetazolamide, a carbonic anhydrase inhibitor, is not included in the standard treatment regimen for HACE, although it is used in the prevention of altitude sickness and in the management of mild forms of AMS. The effectiveness of acetazolamide in the treatment of HACE has been demonstrated occasionally, using a dose of 250 mg administered orally twice a day. Its mechanism of action is based on effects on the proximal renal tubules, inducing metabolic acidosis and stimulating ventilation [4, 41].

Researchers have repeatedly emphasised the importance of prevention; however, once cerebral oedema develops, all rescue efforts should be focused on the rapid implementation of the above-described measures, as without them, most patients die within 24 hours. Treatment and appropriate rehabilitation, lasting several days or weeks, significantly increase the chances of survival, reversal of cerebral oedema, and prevention of permanent neurological deficits.

Summary

HACE is one of the most dangerous complications resulting from exposure to high altitudes. It occurs relatively rarely, but its sudden and rapid progression makes it a life-threatening condition that requires immediate medical attention. The pathomechanisms underlying HACE, although not yet fully understood, are quite complex and involve a number of biochemical and molecular processes, including damage to the blood–brain barrier and the development of vasogenic and cytotoxic oedema.

Individual and environmental factors, such as the rate of acclimatisation, underlying disease burden, and previous episodes of altitude illness, should also be taken into account.

The clinical picture may vary from case to case, but typically begins with non-specific, mild symptoms that can quickly evolve into severe neurological disturbances. It is this ambiguity and the dynamic nature of the patient's condition that make proper diagnosis, recognition, and treatment crucial for determining prognosis. The aforementioned treatment, based mainly on alti-

tude reduction, oxygen therapy, and the administration of dexamethasone in appropriate doses, if implemented promptly, can lead in many cases to complete resolution of symptoms and full recovery.

In summary, high-altitude cerebral oedema remains an interdisciplinary challenge, drawing on knowledge from the fields of neurology, emergency medicine, extreme and travel medicine. Preventive actions, education, and further scientific research into the pathophysiology of the disease are key to improving diagnosis and treatment, and giving patients hope for a full recovery.

References

1. Hackett PH, Oelz O. The Lake Louise consensus on the quantification of altitude illness. In: Sutton JR, Houston CS, Coates G, eds. Hypoxia and Mountain Medicine. Burlington, VT: Queen City Printers; 1992. pp. 327–330
2. Berger MM, Hüsing A, Niessen N, et al. Prevalence and knowledge about acute mountain sickness in the Western Alps. PLoS One, 2023; 18(9): e0291060. doi: 10.1371/journal.pone.0291060
3. Sagoo RS, Hutchinson CE, Wright A, et al.; Birmingham Medical Research and Expedition Society. Magnetic Resonance investigation into the mechanisms involved in the development of high-altitude cerebral edema. J Cereb Blood Flow Metab, 2017; 37(1): 319–331. doi: 10.1177/0271678X15625350
4. Jensen JD, Vincent AL. High Altitude cerebral edema. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 July 17
5. Beall CM. Two routes to functional adaptation: Tibetan and Andean high-altitude natives. Proc Natl Acad Sci U S A, 2007; 104 (Suppl 1): 8655–8660. doi: 10.1073/pnas.0701985104
6. Walsh B, Agrawal S. High-altitude cerebral edema and high--altitude pulmonary edema diagnosed in the desert: a case report. Clin Pract Cases Emerg Med, 2024; 8(3): 202–205. doi: 10.5811/cpcem.3851
7. Basnyat B, Murdoch DR. High-altitude illness. Lancet, 2003; 361(9373): 1967–1974. doi: 10.1016/S0140-6736(03)13591-X
8. Aman M, Alam MS, Khan F, et al. High-altitude cerebral edema manifesting as T2/FLAIR hyperintensity and microbleeds in the white matter on MRI brain. Radiol Case Rep, 2023; 18(5): 1705–1709. doi: 10.1016/j.radcr.2023.01.071
9. Higgins JP, Tuttle T, Higgins JA. Altitude and the heart: is going high safe for your cardiac patient? Am Heart J, 2010; 159(1): 25–32. doi: 10.1016/j.ahj.2009.10.028
10. Falla M, Giardini G, Angelini C. Recommendations for traveling to altitude with neurological disorders. J Cent Nerv Syst Dis, 2021; 13: 11795735211053448. doi: 10.1177/11795735211053448
11. Li Y, Li C, Luo T, et al. Progress in the treatment of high altitude cerebral edema: targeting REDOX homeostasis. J Inflamm Res, 2023; 16: 2645–2660. doi: 10.2147/JIR.S415695
12. Richalet JP, Larmignat P, Poitrine E, et al. Physiological risk factors for severe high-altitude illness: a prospective cohort study. Am J Respir Crit Care Med, 2012; 185(2): 192–198. doi: 10.1164/rccm.201108-1396OC
13. Hackett PH, Roach RC. High altitude cerebral edema. High Alt Med Biol, 2004; 5(2): 136–146. doi: 10.1089/1527029041352054
14. de la Cruz RA, Clemente Fuentes RW, Wonnum SJ, et al. Aerospace decompression illness. [Updated 2024 Jan 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448160/
15. Savioli G, Ceresa IF, Gori G, et al. Pathophysiology and therapy of high-altitude sickness: practical approach in emergency and critical care. J Clin Med, 2022; 11(14): 3937. doi: 10.3390/jcm11143937
16. Xue Y, Wang X, Wan B, et al. Caveolin-1 accelerates hypoxia-induced endothelial dysfunction in high-altitude cerebral edema. Cell Commun Signal, 2022; 20(1): 160. doi: 10.1186/s12964-022-00976-3
17. Wang X, Chen G, Wan B, et al. NRF1-mediated microglial activation triggers high-altitude cerebral edema. J Mol Cell Biol, 2022; 14(5): mjac036. doi: 10.1093/jmcb/mjac036
18. Schoch HJ, Fischer S, Marti HH. Hypoxia-induced vascular endothelial growth factor expression causes vascular leakage in the brain. Brain, 2002; 125(Pt 11): 2549–2557. doi: 10.1093/brain/awf257
19. Shen Y, Gu J, Liu Z, et al. Inhibition of HIF-1α reduced blood brain barrier damage by regulating MMP-2 and VEGF during acute cerebral ischemia. Front Cell Neurosci, 2018; 12: 288. doi: 10.3389/fncel.2018.00288
20. Takata F, Nakagawa S, Matsumoto J, Dohgu S. Blood–brain barrier dysfunction amplifies the development of neuroinflammation: understanding of cellular events in brain microvascular endothelial cells for prevention and treatment of BBB dysfunction. Front Cell Neurosci, 2021; 15: 661838. doi: 10.3389/fncel.2021.661838
21. 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
22. Turner REF, Gatterer H, Falla M, Lawley JS. High-altitude cerebral edema: its own entity or end-stage acute mountain sickness? J Appl Physiol (1985), 2021; 131(1): 313–325. doi: 10.1152/japplphysiol.00861.2019
23. Li S, Zhang Q, Yang C, Zhang F. Mechanism of formation of high altitude cerebral edema: recent advances. Discov Med, 2025; 2: 175. doi: 10.1007/s44337-025-00420-8
24. Gallagher SA, Hackett PH. High-altitude illness. Emerg Med Clin North Am, 2004; 22(2): 329–355, VIII. doi: 10.1016/j.emc.2004.02.001
25. Roach RC, Hackett PH, Oelz O, et al.; Lake Louise AMS Score Consensus Committee. The 2018 Lake Louise Acute Mountain Sickness Score. High Alt Med Biol, 2018; 19(1): 4–6. doi: 10.1089/ham.2017.0164
26. Long C, Bao H. Study of high-altitude cerebral edema using multimodal imaging. Front Neurol, 2023; 13: 1041280. doi: 10.3389/fneur.2022.1041280
27. Imray C, Wright A, Subudhi A, Roach R. Acute mountain sickness: pathophysiology, prevention, and treatment. Prog Cardiovasc Dis, 2010; 52(6): 467–484. doi: 10.1016/j.pcad.2010.02.003
28. Chen T, Wu X, Liu X, Luo F. Reversible leukoencephalopathy with seizures: a case of severe high-altitude cerebral edema. Acta Epileptol, 2024; 6(1): 22. doi: 10.1186/s42494-024-00165-4
29. Kaeley N, Datta SS, Sharma A, G J. Hiccups and slurring of speech: atypical presentation of high-altitude cerebral edema. Cureus, 2023; 15(2): e34997. doi: 10.7759/cureus.34997
30. Bhartiya M, Kumar J, Arora R, Dhiman A. Clinical profile of high-altitude cerebral edema: a case series. Ann Indian Acad Neurol, 2025; 28(2): 257–261. doi: 10.4103/aian.aian_921_24

31. Yarnell PR, Heit J, Hackett PH. High-altitude cerebral edema (HACE): the Denver/Front range experience. Semin Neurol, 2000; 20(2): 209–217. doi: 10.1055/s-2000-9830
32. Bolotin T, Prokopakis KE, Becker B. Atypical high-altitude cerebral edema presentation at an altitude of less than 3000 meters elevation: a case report. Open Access Emerg Med, 2022; 14: 119–122. doi: 10.2147/OAEM.S336951
33. Hackett PH, Yarnell PR, Weiland DA, Reynard KB. Acute and Evolving MRI of high-altitude cerebral edema: microbleeds, edema, and pathophysiology. AJNR Am J Neuroradiol, 2019; 40(3): 464–469. doi: 10.3174/ajnr.A5897
34. Kühn S, Gerlach D, Noblé HJ, et al. An observational cerebral magnetic resonance imaging study following 7 days at 4554 m. High Alt Med Biol, 2019; 20(4): 407–416. doi: 10.1089/ham.2019.0056
35. Velasco R, Cardona P, Ricart A, Martínez-Yélamos S. Vasorreactividad cerebral en el edema cerebral asociado a la altura [Cerebral vasoreactivity in high-altitude cerebral edema]. Neurologia, 2008; 23(1): 65–68
36. Bailey DM, Bärtsch P, Knauth M, Baumgartner RW. Emerging concepts in acute mountain sickness and high-altitude cerebral edema: from the molecular to the morphological. Cell Mol Life Sci, 2009; 66(22): 3583–3594. doi: 10.1007/s00018-009-0145-9
37. Armstrong C. Acute altitude illness: updated prevention and treatment guidelines from the Wilderness Medical Society. Am Fam Physician, 2020; 101(8): 505–507
38. Luks AM, Auerbach PS, Freer L, et al. Wilderness Medical Society Clinical Practice Guidelines for the Prevention and Treatment of Acute Altitude Illness: 2019 Update. Wilderness Environ Med, 2019; 30(4S): S3–S18. doi: 10.1016/j.wem.2019.04.006
39. Zelmanovich R, Pierre K, Felisma P, et al. High altitude cerebral edema: improving treatment options. Biologics, 2022; 2(1): 81–91. doi: 10.3390/biologics2010007
40. Freeman K, Shalit M, Stroh G. Use of the gamow bag by EMT-basic park rangers for treatment of high-altitude pulmonary edema and high-altitude cerebral edema. Wilderness Environ Med, 2004; 15(3): 198–201. doi: 10.1580/1080-6032(2004)15[198:uotgbb]2.0.co;2
41. Wright A, Brearey S, Imray C. High hopes at high altitudes: pharmacotherapy for acute mountain sickness and high-altitude cerebral and pulmonary oedema. Expert Opin Pharmacother, 2008; 9(1): 119–127. doi: 10.1517/14656566.9.1.119