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Examination of novel diagnostic approaches and contemporary strategies for preventing acute mountain sickness

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Abstract

Introduction and purpose:

Acute mountain sickness is caused by hypoxia, of which the brain is the most sensitive. The frequency of occurrence at altitudes above 2500 m above sea level may reach up to 75% of travelers. Prevention of altitude sickness mainly concerns the travel plan and pharmacology. Our study aimed to assess the current literature on altitude sickness, and discuss the possible pathophysiology, epidemiology, and symptoms. Moreover, we underline new guidelines for the treatment, prevention, and diagnosis of altitude sickness in the context of the last guidelines and research. We conducted a PubMed literature review using keywords like "mountaineering sickness" and "altitude sickness". All article types were taken into account: clinical trial, meta-analysis, case report, case series, systematic review, randomized controlled trial, observational study, clinical study, books, and documents in the last 5 years.

A brief description of the state of knowledge:

In recent years, there has been a surge in the accessibility and popularity of high-altitude tourism, emphasizing the need to disseminate information about altitude sickness among travelers. This heightened accessibility has sparked a push for comprehensive research and viable solutions, aiming to address the ramifications of the increased risk associated with such endeavors. Furthermore, there's a growing call for additional research focusing on the unique medical demands posed by tourist excursions and extreme expeditions.

Conclusions:

It underscores the necessity for healthcare professionals equipped with specialized knowledge and expertise in both preventing and treating medical conditions arising in exceptional circumstances.

Keywords: mountaineering sickness, altitude sickness, AMS, acclimatization

INTRODUCTION

Acute altitude sickness is a bodily response triggered by the soaring heights and the resulting oxygen scarcity, a condition that reflects an excessive reactivity to alterations in the environment. Presently, altitudes surpassing the 1500-meter mark above sea level are earmarked as emblematic of high altitude. However, a more nuanced categorization delineates altitude ranges into distinct tiers: spanning from 1500 to 3500 meters above sea level is deemed high altitude; progressing further, the range from 3500 to 5500 meters is classified as very high altitude, while extreme altitudes extend from 5500 to 8850 meters above sea level. Typically, acute mountain sickness (AMS) most frequently emerges at elevations exceeding 2500 meters above sea level.

Beyond its acute manifestation, high-altitude illnesses may manifest in different forms, spanning from subacute conditions like high-altitude pulmonary hypertension to chronic ailments like Monge's disease. Furthermore, the classification extends to include acute altitude sickness (AMS), high altitude cerebral edema (HACE), and high altitude pulmonary edema (HAPE). Notably, severe acute altitude sickness is purported to precipitate the onset of high-altitude cerebral edema (37, 38, 39).

On a global scale, embarking on ascents to non-extreme altitudes, specifically those below 5500 meters above sea level, showcases an incidence rate ranging from 10 to 85%. Intriguingly, observations reveal that at 3500 meters above sea level, over a quarter of individuals contend with acute altitude sickness, a percentage that dramatically escalates to over half of individuals at the formidable altitude of 6000 meters above sea level (37, 39). As an example, among tourists scaling the renowned Kilimanjaro, approximately 47-86% grapple with

acute mountain sickness, and the mortality rate stands at an estimated 1 in 4350 climbers (34).

PATHOGENESIS

While acute altitude sickness and high-altitude cerebral edema share some pathophysiological characteristics, it's crucial to note that the latter isn't simply a more advanced stage of the former. Although their development involves hypoxia-induced processes, their distinct mechanisms are not yet fully comprehended. Acute altitude sickness stems from the body's response to hypoxia at higher elevations. Hypoxia triggers a series of physiological changes, including hypoxemia, wherein decreased oxygen levels in the bloodstream prompt compensatory responses. This decrease in oxygen availability leads to increased cerebrospinal fluid flow, raising the volume and pressure within the skull. Consequently, cerebral blood vessels dilate in an attempt to maintain oxygen supply to the brain. This dilation, coupled with increased permeability of the blood-brain barrier, results in the leakage of fluid and proteins into brain tissue, leading to cerebral edema or brain swelling. The transition from acute altitude sickness to high-altitude cerebral edema marks a critical stage in altitude-related illnesses. While both conditions are linked to oxygen deficiency and share some common pathways, the progression to high-altitude cerebral edema involves a more dangerous manifestation of brain swelling. Understanding these mechanisms is pivotal for effective prevention strategies and timely medical intervention at high altitudes. [38,39]

SYMPTOMS AND MANAGEMENT

When encountering mild symptoms of altitude sickness, it's vital to prioritize caution and maintain your current altitude without further ascent until these symptoms abate. Typically, these mild manifestations, such as headaches or mild nausea, tend to diminish within a span of approximately 18 to 36 hours. During this period, it is advisable to rest, stay hydrated, and allow to adjust to the altitude.

Conversely, if severe symptoms, such as persistent vomiting, severe headaches, confusion, or difficulty in breathing, become apparent, immediate action is essential. Descending to lower altitudes as swiftly as possible is crucial in such instances, and seeking medical assistance becomes paramount. These severe symptoms indicate a potentially dangerous progression and necessitate urgent attention. It is important to note that complete resolution of symptoms might take an extended period, usually spanning from 2 to 5 days, even after descending to lower altitudes. Attempting further ascent during this recovery phase can be perilous, potentially leading to disorientation or, in extreme cases, coma. Therefore, allowing ample time for recovery and acclimatization is pivotal for safety at high altitudes (34, 39, 41).

Tab.1 Division of symptoms of altitude sickness

Mild and moderate symptoms	**Severe symptoms**
mild headache	heavy headache
loss of appetite	chest tightness
nausea	shortness of breath during the rest
vomiting	recurrent vomiting
tiredness	disorientation
weakness	confusion
dizziness	unsteady gait
	inability to maintain balance
	severe cough

The primary treatment for severe altitude sickness revolves around rapid descent from high altitudes, coupled with oxygen therapy. Additionally, medications like acetazolamide, dexamethasone, and nifedipine might be considered as part of the treatment protocol (34).

To prevent altitude sickness, several recommended approaches involve gradual ascent with intermittent rest periods, ascending to higher elevations during the day and descending for sleep, alongside the use of acetazolamide (34, 35). Staying at higher altitudes to acclimatize is emphasized, significantly reducing the risk of developing altitude-related symptoms. Interestingly, the breathing rate and patterns during sleep at the specific altitude where an individual rests become more influential in triggering altitude sickness symptoms than the maximum elevation achieved during the day. It is advised a gradual increase in sleeping altitude, recommending that the elevation for overnight stays should not surpass a gain of 500 meters when positioned above 2500 meters above sea level. Moreover, allowing at least one day for acclimatization at such altitudes is strongly advised to facilitate the body's adjustment to the environment.

Furthermore, engaging in strenuous physical activity and consuming alcohol within the initial 48 hours of reaching higher altitudes, before acclimatization, may provoke the onset of altitude sickness symptoms. Thus, exercising caution during this crucial period is highly recommended.(22, 41)

Mountaineering in high-altitude terrains triggers noteworthy, reversible alterations within the human brain's structure and volume, even when clinical cerebral edema isn't evident. Studies highlight that an extended stay surpassing 4,500 meters above sea level leads to enduring brain changes that persist for over 12 hours post-exposure to such altitudes, with these alterations persisting for at least three days in instances of altitude sickness (19).

The diagnosis of acute altitude sickness primarily revolves around identifying characteristic symptoms, notably the presence of a headache, often accompanied by other typical indicators. Currently, there exist no standardized laboratory or radiological tests for definitive diagnosis. However, the manifestation of nonspecific symptoms, such as diarrhea, warrants consideration of altitude sickness, prompting the need for a comprehensive differential diagnosis. Intriguingly, among ultramarathon runners, occurrences of visual hallucinations above 3,500 meters above sea level didn't consistently align with

the development of acute altitude sickness. Hence, meticulously analyzing symptoms and conducting a detailed evaluation among individuals navigating high altitudes remain crucial (32). Distinguishing altitude sickness from a myriad of other potential medical conditions entails considering a broad spectrum of differential diagnoses, including hypothermia, ischemic stroke, migraine headaches, meningitis, dehydration in children, Rey's syndrome, and sinusitis. It's pivotal to note that the physiological stress induced by diminished oxygen levels can exacerbate pre-existing conditions such as angina, congestive heart failure, and sickle cell anemia. Therefore, an exhaustive and meticulous differential diagnosis stands imperative in delineating altitude sickness from other potentially life-threatening medical conditions prevalent in high-altitude settings.(41)

PHARMACOLOGICAL TREATMENT AND PREVENTION

Acetazolamide is the gold standard of prophylaxis in the treatment of acute altitude sickness. It works by inhibiting the carbonic anhydrase enzyme, causing increased diuresis and compensating respiratory alkalosis. Acetazolamide does not affect the effectiveness of high-altitude endurance exercise at a dose of 500 mg/day.[14] Moreover, the use of acetazolamide in people over 40 years of age improves their visual and motor skills, which slow down while staying at heights.[16] The dose of acetazolamide used is 250-750 mg daily, although even 125 mg is effective in the prevention of mountain sickness and reduces the risk of side effects, but may not provide adequate protection against symptoms. The most common side effects are paresthesia, taste disturbances, and fatigue. [27, 29, 31, 36]

Among the available preparations, climbers also use ibuprofen, which supports brain processes by inhibiting cyclooxygenase. The study by Burns et al. compared the use of ibuprofen and acetazolamide, suggesting that ibuprofen is slightly less effective than acetazolamide. It was noted that it should not be used for fast, high-altitude climbs. Irons et al. noted that ibuprofen and metoclopramide may reduce the severity of headaches, especially those associated with nausea. Regarding the effectiveness of research results of ibuprofen in the prevention of

altitude sickness are divergent, therefore acetazolamide remains the first choice in prevention. [1,2,5,6]

It has been noted that the use of methazolamide may provide more effective protection against the development of altitude sickness, but further research is necessary to confirm the effectiveness of this pharmacotherapy. The action of methazolamide is the same as that of acetazolamide, but it is currently believed that methazolamide has fewer side effects than acetazolamide. Its negative effect on the diaphragm and skeletal muscles, which occurs when using acetazolamide, has not been noticed.[26]

Inhaled budesonide turns out to be ineffective in preventing severe altitude sickness, but it helps reduce blood pressure and increase blood saturation. It may be effective in preventing mild disease.[21,28]

Dexamethasone has not been registered as a treatment for altitude sickness due to its mechanism is poorly understood. Nevertheless, evidence of its effectiveness has been shown in both altitude sickness and high-altitude cerebral edema. It can be also used in some preventive situations.[23,41]

Oral use of vitamin C may reduce hyperuricemia at high altitudes. The increase in uric acid concentration increases over a month when changing altitude from low to high, and vitamin C at a dose of 500 mg/day effectively reduced the amount of uric acid in the blood serum and can alleviate the symptoms of altitude sickness.[25]

The use of trimetazidine to relieve the symptoms of altitude sickness is ineffective. The use of this preparation relieves altitude fatigue, which may be a component of altitude sickness, but does not affect other symptoms.[17]

In recent years, there has been speculation about the effectiveness of repeated remote ischemic preconditioning (RIPC) as a pre-exposure treatment. Whang et al. observed that a 4-week regimen of RIPC reduced the severity and frequency of altitude sickness. However, Berger et al. noted that RIPC applied immediately before increasing altitude had no effect on reducing the symptoms of altitude sickness. The results from individual centers are divergent, although the discrepancies are explained by unsystematized treatment patterns.[3,4]

Limper and colleagues evaluated the use of the 30° elevated sleep method. They did not notice a reduction in the risk of developing altitude sickness despite

the impact on the pathogenesis of cerebrospinal fluid displacement. This method was also not effective in improving climbers' sleep or reducing hypoxia. [12]

The use of the apnea training method, which involves extending the maximum breath hold, turns out to be ineffective in preventing symptoms when climbing at altitudes of up to 5,000 m above sea level. [24]

The impact of physical activity at high altitudes was also analyzed as potentially increased the chances of acclimatization in a shorter time. No difference was noticed among climbers engaged in sports activity on individual sections and those without additional moderate physical activity.[33]

RISK FACTORS

The emergence of altitude sickness is significantly influenced by various critical factors, including the pace at which climbers ascend, the duration of their stay at elevated heights—especially during sleep—and individual-specific characteristics (39). These factors intertwine, shaping the vulnerability of individuals to the onset of altitude-related maladies.

Empirical evidence suggests a heightened prevalence of altitude sickness among women, as highlighted across multiple studies (8, 9, 11). However, the consensus on the relationship between gender and susceptibility to altitude sickness remains disparate, with some investigations failing to establish a definitive correlation.

Age, as a determinant factor in altitude sickness, remains a topic fraught with incongruity. While certain studies propose a potential link between younger age and increased susceptibility (10), these findings lack a conclusive trajectory (7, 9). Notably, the administration of acetazolamide has been identified as an influential factor in negating the influence of youth as a significant risk factor, as indicated by Richalet et al. (11).

Endurance-trained mountaineers exhibit a unique susceptibility to expedited ascent beyond 3,450 meters above sea level. This heightened susceptibility is attributed to the intensified activity of the sympathetic nervous system and an elevated metabolic rate, both characteristics stemming from their rigorous training regimen (20).

Addressing concerns stemming from the COVID-19 pandemic, preliminary findings suggest that a history of mild COVID does not inherently elevate the risk of succumbing to altitude sickness. Consequently, individuals with a recent history of mild COVID should not perceive it as a prohibiting factor in engaging in mountainous expeditions (18).

DIAGNOSTIC METHODS

At present, diagnosing altitude sickness solely relies on clinical symptoms, lacking effective and easily accessible diagnostic tools. This dearth has spurred an earnest quest for more sensitive and specific tests, leading to active research in novel diagnostic methodologies.

Chang et al. introduced a novel approach involving a wireless device that monitors electroencephalographic changes, potentially indicating the onset of acute altitude sickness. However, limitations persisted in this study, including a limited participant pool and challenges in data collection during climbing expeditions. Acknowledging these constraints, the authors underscored the need for further refinement and progression of this diagnostic avenue in subsequent studies (13).

An intriguing avenue investigated the utilization of smartwatch technology to predict acute altitude sickness by quantifying maximum oxygen consumption. Researchers conducted meticulous assessments, employing both smartwatch tests and cardiopulmonary exercise tests, measuring oxygen intake at varying altitudes - from a low of 300 meters to a substantial height of 3900 meters. Impressively, this method demonstrated applicability not only at lower altitudes but also extended its potential utility up to heights as formidable as 3,500 meters above sea level. Yet, establishing validated systems compatible with smartwatch devices remains an ongoing imperative for accurate and dependable assessments (15).

These innovative pursuits in employing modern technology, like wireless monitoring devices and smartwatches, signify promising strides toward developing more sophisticated and easily applicable diagnostic tools tailored for altitude sickness. Nevertheless, rigorous validation and continued research are paramount to fortify the reliability and practicality of these diagnostic methods for broader implementation across high-altitude settings.

SUMMARY

The surge in interest surrounding high-altitude tourism has propelled dedicated research efforts towards countering the challenges posed by altitude sickness. Within this burgeoning field, there's a keen pursuit of diagnostic methodologies that not only meet the critical trifecta of affordability, accuracy, and ease of application but also stand as reliable tools in identifying and preempting this condition. Concurrently, researchers are directing significant focus towards optimizing the dosages of established medications while delving into innovative therapeutic avenues aimed at both prevention and treatment.

The domain of high-altitude medicine necessitates a profound comprehension among healthcare practitioners. This encompasses a comprehensive understanding of effective treatments, strategies for prevention, and the intricate art of differential diagnosis specifically tailored for elevated altitudes. The urgency underlying this need stems from the mounting numbers of individuals engaging in high-altitude adventures, where acute mountain sickness looms as a formidable adversary, capable of instigating severe complications. The role of knowledgeable and well-prepared medical professionals becomes pivotal in ensuring the safety and welfare of those exposed to such altitudinal challenges.

It is imperative to underscore the multifaceted nature of individual-specific factors as primary risk elements associated with altitude-related maladies. This accentuates the critical need for meticulous scrutiny of symptoms and a thorough exploration of potential differential diagnoses, thereby enabling early-stage identification and intervention.

Moreover, a noteworthy facet emerges: the potential onset of acute mountain sickness can occur at altitudes lower than the conventional threshold of 2500 meters above sea level. This revelation necessitates a recalibration of awareness, as it underscores the potential susceptibility of not just tourists but also extreme athletes to this condition even in seemingly moderate altitudes, demanding a broader consideration in health assessments.

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