476e Altitude Illness

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EPIDEMIOLOGY

Mountains cover one-fifth of the earth's surface; 38 million people live permanently at altitudes ≥2400 m, and 100 million people travel to high-altitude locations each year. Skiers in the Alps or Aspen; religious pilgrims to Lhasa or Kailash; trekkers and climbers to Kilimanjaro, Aconcagua, or Everest; and military personnel deployed to high-altitude locations are all at risk of developing acute mountain sickness (AMS), high-altitude cerebral edema (HACE), high-altitude pulmonary edema (HAPE), and other altitude-related problems. AMS is the benign form of altitude illness, whereas HACE and HAPE are life-threatening. Altitude illness is likely to occur above 2500 m but has been documented even at 1500–2500 m. In the Mount Everest region of Nepal, ~50% of trekkers who walk to altitudes >4000 m over ≥5 days develop AMS, as do 84% of people who fly directly to 3860 m. The incidences of HACE and HAPE are much lower than that of AMS, with estimates in the range of 0.1–4%.

PHYSIOLOGY

Ascent to a high altitude subjects the body to a decrease in barometric pressure that results in a decreased partial pressure of oxygen in the inspired gas in the lungs. This change leads in turn to less pressure driving oxygen diffusion from the alveoli and throughout the oxygen cascade. A normal initial "struggle response" to such an ascent includes increased ventilation—the cornerstone of acclimation—mediated by the carotid bodies. Hyperventilation may cause respiratory alkalosis and dehydration. Alkalosis may depress the ventilatory drive during sleep, with consequent periodic breathing and hypoxemia. During early acclimation, renal suppression of carbonic anhydrase and excretion of dilute alkaline urine combat alkalosis and tend to bring the pH of the blood to normal. Other physiologic changes during normal acclimation include increased sympathetic tone; increased erythropoietin levels, leading to increased hemoglobin levels and red blood cell mass; increased tissue capillary density and mitochondrial numbers; and higher levels of 2,3-bisphosphoglycerate, enhancing oxygen utilization. Even with normal acclimation, however, ascent to a high altitude decreases maximal exercise capacity (by ~1% for every 100 m gained above 1500 m) and increases susceptibility to cold injury due to peripheral vasoconstriction. Finally, if the ascent is made faster than the body can adapt to the stress of hypobaric hypoxemia, altitude-related disease states can result.

GENETICS

Hypoxia-inducible factor, which is important in high-altitude adaptation, controls transcriptional responses to hypoxia throughout the body and is involved in the release of vascular endothelial growth factor (VEGF) in the brain, erythropoiesis, and other pulmonary and cardiac functions at high altitudes. In particular, the gene *EPAS1*, which codes for transcriptional regulator hypoxia-inducible factor 2α, appears to play an important role in the adaptation of Tibetans living at high altitude, resulting in lower hemoglobin concentrations than are found in the Han Chinese. For acute altitude illness, a single gene variant is unlikely to be found, but the differences in the susceptibility of individuals and populations, familial clustering of cases, and a positive association of some genetic variants all clearly support a role for genetics. Approximately 58 candidate genes have been tested, and at least one variant from 17 of these genes is associated with altitude illness.

ACUTE MOUNTAIN SICKNESS AND HIGH-ALTITUDE CEREBRAL EDEMA

AMS is a neurologic syndrome characterized by nonspecific symptoms (headache, nausea, fatigue, and dizziness), with a paucity of physical findings, developing 6–12 h after ascent to a high altitude. AMS is a clinical diagnosis. For uniformity in research studies, the Lake Louise Scoring System, created at the 1991 International Hypoxia Symposium, is generally used. AMS must be distinguished from exhaustion, dehydration, hypothermia, alcoholic hangover, and hyponatremia. AMS and HACE are thought to represent opposite ends of a continuum of altitude-related neurologic disorders. HACE (but not AMS) is an encephalopathy whose hallmarks are ataxia and altered consciousness with diffuse cerebral involvement but generally without focal neurologic deficits. Progression to these signal manifestations can be rapid. Papilledema and, more commonly, retinal hemorrhages may also develop. In fact, retinal hemorrhages occur frequently at ≥5000 m, even in individuals without clinical symptoms of AMS or HACE. It is unclear whether retinal hemorrhage and cerebral hemorrhage at high altitude are caused by the same mechanism.

Risk Factors The most important risk factors for the development of altitude illness are the rate of ascent and a prior history of high-altitude illness. Exertion is a risk factor, but lack of physical fitness is not. An attractive but still speculative hypothesis proposes that AMS develops in people who have inadequate cerebrospinal capacity to buffer the brain swelling that occurs at high altitude. Children and adults seem to be equally affected, but people >50 years of age may be less likely to develop AMS than younger people. Aging appears to be associated with blunting of cardiac chronotropic function and an increase in ventilatory response leading to maintenance of arterial oxygen saturation in hypoxia. Most studies reveal no gender difference in AMS incidence. A recent study showed that, in women, adaptive responses to hypoxia with aging are blunted by menopause but can be maintained with endurance training. Sleep desaturation—a common phenomenon at high altitude—is associated with AMS. Debilitating fatigue consistent with severe AMS on descent from a summit is also an important risk factor for death in mountaineers. A recently published prospective study involving trekkers and climbers who ascended to altitudes between 4000 m and 8848 m showed that high oxygen desaturation and low ventilatory response to hypoxia during exercise are independent predictors of severe altitude illness. However, because there may be overlap between groups of susceptible and nonsusceptible individuals, accurate cutoff values are hard to define. Prediction is made more difficult because the pretest probabilities of HAPE and HACE are low. Neck irradiation or surgery damaging the carotid bodies, respiratory tract infections, and dehydration appear to be other potential risk factors for altitude illness.

Pathophysiology The exact mechanisms causing AMS and HACE are unknown. Evidence points to a central nervous system process. MRI studies have suggested that vasogenic (interstitial) cerebral edema is a component of the pathophysiology of HACE. In the setting of high-altitude illness, the MRI findings shown in Fig. 476e-1 are confirmatory of HACE, with increased signal in the white matter and particularly in the splenium of the corpus callosum. Quantitative analysis in a 3-tesla MRI study revealed that hypoxia is associated with mild vasogenic cerebral edema irrespective of AMS. This finding is in keeping with case reports of suddenly symptomatic brain tumors and of cranial nerve palsies without AMS at high altitudes. Vasogenic edema may become cytotoxic (intracellular) in severe HACE.

Impaired cerebral autoregulation in the presence of hypoxic cerebral vasodilation and altered permeability of the blood-brain barrier due to hypoxia-induced chemical mediators like histamine, arachidonic acid, and VEGF may all contribute to brain edema. In 1995, VEGF was first proposed as a potent promoter of capillary leakage