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HEADACHE (R.B. HALKER SINGH, SECTION EDITOR)

Sherpas, Coca Leaves, and Planes: High Altitude and Airplane Headache Review with a Case of Post-LASIK Myopic Shift

Shivang G. Joshi[1] · Laszlo L. Mechtler[1]

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Abstract

Purpose of Review High altitude headache is a common neurological symptom that is associated with ascent to high altitude. It is classified by the International Classification of Headache Disorders, 3rd Edition (ICHD-3) as a disorder of homeostasis. In this article, we review recent clinical and insights into the pathophysiological mechanisms of high altitude and airplane headache. We also report a second case of post-LASIK myopic shift at high altitude exposure secondary hypoxia. Headache attributed to airplane travel is a severe typically unilateral orbital headache that usually improves after landing. This was a relative recent introduction to the ICHD-3 diagnostic criteria. Headache pain with flight travel has long been known and may have been previously considered as a part of barotrauma. Recent studies have helped identify this as a distinct headache disorder.

Recent Findings Physiologic, hematological, and biochemical biomarkers have been identified in recent high altitude studies. There have been recent advance in identification of molecular mechanisms underlying neurophysiologic changes secondary to hypoxia. Calcitonin gene–related peptide, a potent vasodilator, has been implicated in migraine pathophysiology. Recent epidemiological studies indicate that the prevalence of airplane headache may be more common than we think in the adult as well at the pediatric population. Simulated flight studies have identified potential biomarkers.

Summary Although research is limited, there have been advances in both clinical and pathophysiological mechanisms associated with high altitude and airplane headache.

Keywords High altitude headache · Hypoxia · Acute mountain sickness · Airplane Headache · Sinus barotrauma · Headache disorder attributed to homeostasis

Personal Case of Post-LASIK Myopic Shift at High Altitude from author LM

At the age of 16, I was diagnosed of having nearsightedness, which caused me to wear contact lenses. I was an avid soccer player all of my life and played in Europe and was dependent on contact lenses to see. When the opportunity came to climb Mt. Kilimanjaro in Tanzania, Africa, for a fundraiser with my patients and colleagues, I did not want to climb with glasses or contact lenses, so I began considering laser-assisted in situ keratomileusis (LASIK) surgery.

After thorough research of LASIK and meeting with the ophthalmologist, I was reassured that there should not be any complications with having the surgery and then climbing the mountain (high altitude), so, I had the LASIK completed. In 2007, just 3 weeks after having surgery, with a team of 20, I climbed the mountain.

On the mountain, it took 6 days to summit. I had no issues with the climb, except for the fact that it was physically much more difficult than expected. I was 48 years old at the time and did not have any visual issues up until approximately 500 feet from the summit. At 19,000 feet, I started noticing blurry vision. This was obvious to my colleagues because I was stumbling to reach the summit. That day, we started climbing at midnight and, essentially, we were summiting during sunrise. I knew I was having issues because I was acting as the photographer for the group and I was unable to focus the camera as the sun was rising.

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✉ Shivang G. Joshi
sjoshi@dentinstitute.com

[1] DENT Neurological Institute, 3890 Sheridan Drive, Amherst, NY 14226, USA

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Mt. Kilimanjaro (19,340 ft)

At this point, the guide told me that I should return to base but I whispered to him to hold my arm and take me to the summit, which was another 340 feet. At 19,340 feet, as the sun came out, it was obvious that I was having significant visual symptoms. I was unable to see my hand in front of my eyes, but I did see a halo of light around it. At that time, I notified my fellow climbers who sat me down at the summit for a period of 30 min. I did not have a headache, eye pain, and I did not feel nauseous in any way. Although my breathing rate was about 40 respirations per minute, I did not have any chest issues or shortness of breath.

Two of my African guides did assist me and brought me down the mountain. During this time, I lost most of my toenails because of traumatic injury, not being able to see what was in front of me. As I decreased by every 1000 feet, I noticed that my vision was improving about 10%, so, when we went down 5000 feet, there was a 50% improvement of my vision, which was something that reassured me that there would not be any long-term side effects. I was not overly concerned because of the lack of headaches or eye pain. I thought that I was potentially suffering from corneal edema.

When I reached the camp at 5000 feet, my vision was 80–90% returned. What is most interesting about this whole episode was that afterwards, from age 48 to now at 60, I do not wear any corrective lenses for nearsightedness or farsightedness. In other words, for the first time in my life, essentially, I am without corrective lenses. I call this "killy eyes" because somehow, the ocular insult that occurred at 19,000 feet either changed the shape of my lens or did something that made my eyes normal.

Introduction

High altitude headache (HAH) is coded in the International Classification of Headache Disorders, 3rd Edition (ICHD-3) among headaches attributed to headache disorders of homeostasis [1]. Clinically, the headache is bilateral, worse with exertion, mild to moderate in intensity, and associated with nausea. Typical other migraine features are not present. Headache is a common feature of acute mountain sickness (AMS), which may also include gastrointestinal, respiratory, sleep disturbance, and dizziness. About 80% of those what ascent to high altitude have a headache [2]. Response to oxygen can be a distinguishing factor from migraines.

Diagnostic criteria (HAH):

A. Headache fulfilling criterion C

B. Ascent to altitude above 2500 m has occurred

C. Evidence of causation demonstrated by at least two of the following:

1. Headache has developed in temporal relation to the ascent

2. Either or both of the following

a) Headache has significantly worsened in parallel with continuing ascent

b) Headache has resolved within 24 h after descent to below 2500 m.

3. Headache has at least two of the following three characteristics

a) Bilateral location

b) Mild or moderate intensity

c) Aggravated by exertion, movement, straining, coughing, and/or bending

D. Not better accounted for by another ICHD-3 diagnosis

Headache attributed to airplane travel (AH) is typically unilateral, orbital, severe, and caused by airplane travel and improves after landing [1]. One of the earliest accounts is from 1783 where a hydrogen-filled balloon while ascent resulted in severe ear and jaw pain. This was initially attributed to an imbalance between external air pressure and middle ear resulting in sinus barotrauma. In 2004, the term airplane

"Dead Woman's Pass" highest point on the Inca Trail (13,828ft)

headache was described in a case of headaches associated with takeoff and landing without the presence of sinus disease [3].

Diagnostic criteria (AH):

A. At least two episodes of headache fulfilling criterion C

B. The patient is traveling by airplane

C. Evidence of causation demonstrated by at least two of the following:

1. Headache has developed during the airplane flight
2. Either or both of the following

a) Headache has worsened in the temporal relation to ascent following take off and/or descent prior to landing of the airplane

b) Headache has spontaneously improved within 30 min after the ascent or descent of the airplane is completed

3. Headache is severe, with at least two of the following three characteristics:

a) Unilateral location[1]

b) Orbitofrontal location[2]

c) Jabbing or stabbing quality[3]

D. Not better accounted for by another ICHD-3 diagnosis[4]

Notes: 1.Side shift between different flights occurs in around 10% of cases

2. Parietal spread may occur

3.Pulsation (throbbing) may also be noted

4. In particular, sinus disorder should be excluded

High Altitude Headaches

History of migraines has been identified as a risk factor for development of HAH [4]. In this study, HAH occurred in 39% of hikers and AMS in 26% of hikers even though the median elevation for the residence for the subjects was 1697 m. History of migraine resulted in any headaches at altitude (OR 2.49, 95% CI 1.62–3.65), whereas there was a stronger association with migraine (OR 14.05, 95% CI 5.49–35.93).

Optic nerve edema at high altitude can occur independent of AMS [5]. Researchers found increased optic nerve sheath diameter was related to hypoxic changes at high altitude. This increase is not directly related to development of optic disc edema, which is a well-characterized phenomenon of high altitude exposure. Retinal and venous distension on ophthalmic exam may also be a hypoxic risk factor for HAH [6]. Retinal hemorrhages are also common. Monocular vision loss can be from decreased blood supply to the retina. However, decreased in blood supply to the visual cortex may also result in cortical blindness.

In a LASIK procedure, a small flap is cut in the corneal surface resulting in correction of nearsightedness. Post-surgical refraction does not typically shift with altitude changes. To the best of our knowledge, the case noted above by author (LM) is only the second to be reported of its kind. The first case of myopic shift post-LASIK involved a 52-year-old post-LASIK patient who, at 18,000 feet, developed noticeable myopia and clarity reduced to only 20 feet. His vision improved with descent to 10,000 feet. The mechanism was thought to be due to increased corneal hydration at normobaric hypoxia. The authors also note that anterior radial fibers are severed when a flap is made and this results in "anterior corneal steepening" with the myopic shift [7•]. A case of myopic shift in a corneal graft at high altitude has also been observed. Here it was suggested that hypoxic environments may induce corneal curvature changes in stable transplant patients [8].

Machu Picchu, Peru

A large population-based study in Nepal with about 21,000 subjects suggested that living at higher elevations was associated higher prevalence of migraines as well as increased severity of symptoms [9]. These findings corroborated an earlier small pilot Peruvian study, suggesting an association between chronic exposure to altitude and migraines [10•].

A recent study in young Chinese males identified higher heart rate and lower SpO_2 as risk factors for the development of HAH [11••]. Lower BUN at lower or higher altitude was an independent risk factor for HAH. In this observational study, 318 males ascended from sea level, 50 m to an altitude of 3700 m by train over a 72-h period. Physiological and biochemical parameters were assessed one week prior to and 24 h after study. No hematological associations were observed.

Multiple other neurologic events/(mechanisms) have been reported at higher altitudes including transient ischemic attacks (vasospasm or vasoconstriction), cerebral infarction (hypoxic induced polycythemia), cerebral venous thrombosis (dehydration, polycythemia), seizures (hypocapnia), and cranial nerve palsies, most commonly sixth (cerebral edema) among others [12].

Pathophysiology of High Altitude Headaches

Cellular hypoxia is a common end result from multiple different mechanisms.

Clinical symptoms may vary from individuals [12]. Between 1500 and 3500 m (high altitude), one may experience AMS, high altitude cerebral edema (HACE), slowing to complex reactions, and psychomotor slowing. Between 3500 and 5500 m (very high) learning and spatial memory

Machu Picchu, Peru

impairment, > 5500 m (extreme altitude) recall impairment, MRI white matter changes above 7000 m and hallucinations above 7500 m. As a reference, the peak of Mt. Kilimanjaro is 5895 m and Mt. Everest 8848 m. HACE is typically treated with rapid decent and dexamethasone.

There have been recent advances in our understanding of mechanisms underlying AMS and HACE. There is increased blood brain barrier permeability at higher altitude. Underlying mechanism of HACE may be due to a combination of cytotoxic (intracellular) and/or vasogenic (extracellular) edema. Diffusion-weighted MRI imaging may help identify the mechanism. Cytotoxic edema may be from failure of the Na^+/K^+ ATPase failure; free radical formation may lead to vasogenic edema leading to further basement membrane degradation. Localized hyperkalemia can increase calcium and intern increase nitric oxide, causing vasodilation [12].

Calcitonin gene–related peptide (CGRP), a potent cerebral vasodilator, has been implicated in the activation of the trigeminal vascular system and migraine pathophysiology [13••]. Other physiologic changes that may be a contributing factor include increase in adenosine [14].

In general, the higher the altitude, the proportion of oxygen remains the same but the partial pressure is decreased resulting in decreased availability to tissue. Initially, hyperventilation, tachycardia and polycythemia, and increased blood flow can maintain the oxygen needs of the brain. Over a period of time acclimation can occur by increases in red blood cells. PET studies suggest that indigenous persons living at higher altitude have lower glucose metabolism in the frontal cortex, suggesting a protective mechanism from chronic low oxygen states [15].

A prospective study of 77 volunteers simulated high altitude (4500 m) by regulated normobaric hypoxia (F_IO_2 = 12.6%) to evaluate AMS. It is well known that hypoxia can trigger migraines in patients with a history of migraines. However, in this study, hypoxia was found to be a trigger for HAH and migraine-like headaches in non-migraine, healthy volunteers [16].

Treatment

There is no data currently to suggest that newer migraine CGRP monoclonal antibodies can have a protective benefit for HAH. Mechanistically, it is an interesting area that needs further exploration. HAH may improve with oxygen supplementation or within 24 h after decent. Ironically, one study noted headache from rapid decent from altitude by car from a median altitude of 1920 m as well as rapid decent by 2 individuals in an elevator [17].

Simple analgesic medications such as ibuprofen and acetaminophen may help with mild symptoms of HAH. A systemic review and meta-analysis suggest that ibuprofen with doses of up to 600 mg three times daily may be a preventive alternative to acetazolamide or dexamethasone [18].

Acetazolamide is a carbonic anhydrase inhibitor and may result in metabolic acidosis. Protective benefit may be related to decrease in production of cerebrospinal fluid. Typical doses for acetazolamide are 125 to 250 mg twice per day. It can be administered the day or night before ascent. A recent study looking at administration of acetazolamide the day of ascent showed a slightly higher rate of AMS [19]. Clinically obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease are associated with acute exacerbations of hypoxemia on chronic hypoxemia. Acetazolamide has been found to increase cerebral oxygenation in OSA patients [20].

Other diuretics such as furosemide are more useful for acute treatment of cerebral edema versus prevention. There is no definitive benefit with the use of migraine medications such as sumatriptan [21]. Ginko biloba herbal remedies have mixed results [22].

While acetazolamide is used to prevent AMS, dexamethasone can also be used to treat cerebral edema. Adverse reaction from dexamethasone may include adrenal suppression, hyperglycemia, insomnia, psychiatric side effects, avascular necrosis of the femoral head, renal, and GI injury. Headache is a common adverse reaction to phosphodiesterase 5 inhibitors such as tadalafil and sildenafil. However, they can be useful in the treatment of high altitude induced pulmonary edema by reducing pulmonary hypertension [23, 24].

Personal Anecdote From Author SJ

In the late 1990s, I embarked on a classical 4-day trek through the Andes, on the famous Inca Trail to Machu Picchu, Peru. I first landed in Cusco, Peru, to acclimate, about 3200 m. I rested, hydrated, and acclimated for about 48 h. Our starting point was at 2600 m near the Urabamba River. There is some variability in the elevation throughout the 28-mile trek, with an ascent to 3600 m on the first day. The second day ascends over Warmi Wanusqa or "Dead Woman's Pass," resembling a woman in a supine position, the highest point on the trail (4200 m). From there on, the trail descends until it arrives at Machu Picchu (2430 m). At points during the trek, I remember having to stop, rest, and catch my breath every 10 min or so. Every morning we were offered a "coca tea." This consisted basically of a few coca leaves in hot water. During the trek, we also periodically chewed on the leaves. I recalled a minimal anesthetic sensation in the lips and mouth region, presumably due to effects of various alkaloids found in the leaves. We were told these measures would help with altitude sickness. Nights were very cold, hailed on our tents one night. Each day, we would pass by ancient ruins, views of snow capped mountain peaks, and various flora and fauna with climate changes. On the last day, the exhaustion almost seemed surreal.

A cross-sectional study evaluated the epidemiology and impact of AMS in tourists visiting Cusco, Peru. Out of 991 travelers, only 29.1% had travel advice from a physician, and 19% were given some advice on acetazolamide. Coca leaf products, in the form of raw leaves chewed or as tea, were used by 62.8% vs. 16.6% of travelers who took acetazolamide to prevent AMS. AMS was reported by 48.5%, and 17.1% had severe symptoms. Travelers older than 60, recent high altitude exposure, having visited lower altitude cities, or used acetazolamide were less likely to develop AMS. On the contrary, use of coca leaves was associated with increased frequency [25].

The wilderness society practice guideline includes coca as "other option." The authors conclude that due to limited data, proven agents should be used first for AMS prevention. Indigenous persons living at higher altitudes for centuries have used coca leaves. Cocaine is the main alkaloid found in coca plants, among18 others. However, an insignificant amount is ingested by chewing or in a tea [26].

A small study looked at biochemical and physiologic changes of chewing coca leaves. They found that coca leaves blocked glycolytic pathways resulting in increase in glucose and pyruvate. Chewing coca leaves during exercise was thought to provide sustained benefits [27]. There is scant data on the use of cannabis in HAH or AMS.

Airplane Headache

A recent multiheadache center Italian population–based study identified the prevalence of AH to be 4.0% (30/733). In a small proportion of patients, similar attacks were also triggered by decompression phase of diving and rapid decent from altitude by car. They hypothesized an imbalance between intra-sinus and external pressure [28]. In an earlier Danish study, the prevalence was about 8.3% and higher in those who had a history of HAH [29].

AH is not uncommon in the pediatric populations. In a multicenter study, out of 320 children with a history of a primary headache disorder, 4.7% had AH. Most were females and localization was bilateral, and symptoms occurred at anytime during flight [30].

Several other case reports can be found in the literature. A recent systematic review of 39 articles identified 275 total patients (45% females and 54% males). The mean diagnosis age and age at first attack were about 28 and 26 respectively. Unlike the pediatric population, majority of the pain in adults is unilateral, frontal, orbital, severe, and lasts about 30 min. Majority occurred during decent. There appeared to be no relationship between migraine and AH in this study [31].

Pathophysiology of Airplane Headaches

A simulated airplane headache study was conducted in an attempt to identify underlying mechanisms [32]. AH patients (14) matched with health controls (7) entered a pressure chamber that simulated an airplane flight. The participants in the AH group experienced a typical attack while the non-AH group did not. Prostaglandin E2 (PGE_2), cortisol, and saturation pulse oxygenation (SPO) alterations were observed in the AH group vs. controls, suggesting a potential role as biomarkers. There was a higher increase in PGE_2, in the AH group post-stimulation. Underlying mechanism may be related to effects on cerebral vasodilation. Future studies infusing PGE_2 in AH patients may be helpful. Cortisol levels were elevated for the AH group during simulation, possibly related to greater anxiety in the group. The oxygen saturation dropped lower for the AH group in the chamber. It was unclear if there is a relationship between low saturation and headache or if the AH group is more sensitive to atmospheric pressure changes. However, decreased barometric pressure changes have been associated with migraines [33]. Other chronic pain conditions such as rheumatoid and osteoarthritis may also have an association [34–36]. Although exact mechanism remains unclear, barometric pressure sensors in the vestibular region may play a role. Animal research shows that lowered barometric pressure induce stress signals stimulating trigeminal nerve endings in the dura to release neuropeptides such as CGRP [37].

Sinus barotrauma or "sinus squeeze" or barosinusitis have been implicated in the mechanism of AH. Trigeminal nerve endings innervate the ethmoid sinuses, possibly explaining the frontal and orbital nature of the pain [38].

A case of a 74-year-old woman who presented with thunderclap headache during airplane decent was subsequently diagnosed with reversible cerebral vasoconstriction syndrome (RCVS) [39]. RCVS is under diagnosed in the general population, and it may be possible that "low-grade" RCVS is an underlying mechanism for AH with atypical longer duration symptoms.

Treatment of Airplane Headache

Non-pharmacological approach, including applying pressure to painful area to chewing and extension of the earlobe, has been tried to alleviate the pain associated with AH with limited success [40••].

Pharmacological agents such as naproxen, ibuprofen, and triptans have been used with some efficacy; however, rigorous clinical trials are needed [29, 31, 40••, 41]. Mechanisms may be related to their anti-inflammatory effects on PGE_2 and cyclooxygenase. In my anecdotal observations, patients using oral or nasal decongestants did find some preventive benefit.

Conclusion

There are some overlaps with AH and HAH. Recent identifications of physiologic and biochemical biomarkers in HAH may allow for better preparedness and development of specific treatments. We add to the literature by reporting a second case of post-LASIK, reversible myopic shift changes at high altitude. Further epidemiological assessment is needed.

Airplane travel has become more frequent and AH may be under diagnosed. A difference in clinical presentation in the pediatric population may suggest an underlying anatomical role. Potential underlying pathophysiological mechanisms such as low-grade RCVS need to be further studied. There is no current data on the use of CGRP antibodies for the treatment or prevention of AH or HAH. The mechanistic potential is interesting and should be a future area of research. Larger multicenter studies are needed in order to better characterize both airplane and high altitude headaches.

Compliance with Ethical Standards

Conflict of Interest Shivang G. Joshi and Laszlo Mechtler each declare no potential conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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