HIGH-ALTITUDE RETINOPATHY: A REVIEW

Although rare and generally self-limiting, this condition may be associated with more serious disease.

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Millions travel to high-altitude destinations each year without fully understanding the potential medical risks involved. High-altitude illnesses, including acute mountain sickness (AMS), high-altitude cerebral edema (HACE), high-altitude pulmonary edema, and high-altitude retinopathy (HAR), are associated with the hypobaric nature of high altitudes. These conditions are commonly observed at altitudes greater than 2,500 m (8,200 ft) in non-acclimatized individuals shortly after ascent and may be caused by hypobaric hypoxia-induced compensatory mechanisms to boost delivery of oxygen.1,2

HAR DEFINED

HAR was first described in 1969 by Singh et al,3 who noted increased dilatation and tortuosity of retinal vasculature, along with scattered dot-blots and flame-shaped hemorrhages, in 24 (1.3%) of 1,925 patients who were diagnosed with AMS after ascending to between 3,353 m and 5,486 m above mean sea level.3

HAR is usually asymptomatic and self-limiting, with most manifestations resolving spontaneously after descent.4 Typically, HAR occurs in individuals who ascend above 2,500 m but can occur at as low as 2,000 m.5-7 Symptomatic patients may experience unilateral or bilateral decreased vision, scotoma, and/or sudden onset of floaters after 8 to 24 hours of high-altitude exposure (see Case Example of HAR).6,8 Severe manifestations rarely occur, but isolated cases of anterior ischemic optic neuropathy, branch retinal artery occlusion, central retinal vein occlusion, cilioretinal artery occlusion, and cystoid macular edema have been reported with poor visual recovery.9,10-14

RISK AND INCIDENCE

Risk factors for HAR include rapid ascent, high maximum altitude, high baseline IOP, genetic susceptibility, and use of NSAIDs.7,15 HAR has been reported more frequently in individuals of young age, and its prevalence varies widely. McFadden et al noted retinal hemorrhages in 56% of 39 healthy individuals after a stay at 5,360 m,16 whereas Barthelmes et al reported an incidence of up to 79% of 28 climbers during a high-altitude expedition.17

PATHOPHYSIOLOGY

Various theories have been proposed to elucidate the pathogenesis of HAR. Hypobaric hypoxia experienced at a high altitude induces various compensatory mechanisms aimed to maintain oxygen delivery, and it is thought that inadequate autoregulatory response of the retinal vascular system is the primary cause of HAR.17,18 That is, hypoxia is assumed to cause increased retinal blood flow and intravenous pressure secondary to intracranial pressure, variations in hematocrit levels, extreme physical exertion, and Valsalva maneuvers during mountain climbing at high elevation. A hypoxic vasodilatation exposed to increased retinal venous pressure leads to a predisposition to intraretinal hemorrhages.9,17 Reduced IOP at high altitudes may also contribute to the progression of intraretinal hemorrhages.19 Moreover, the increase of cerebral vascular blood flow and disruption of the blood-brain barrier caused by hypoxia can lead to cerebral edema, which results in optic disc swelling.20

INVESTIGATING THE MECHANISMS

Xin et al conducted a randomized study that explored the effects of hypobaric hypoxia on the retinas of rats to investigate whether resveratrol has a protective effect on hypoxic damage.21 The study concluded that hypobaric hypoxia increased thioredoxin 1 and thioredoxin 2 expression in the retina, and resveratrol treatment significantly reversed these findings (P < .05 and P < .05, respectively). Therefore, resveratrol may be beneficial as a treatment
for HAR by exerting an antioxidative role and modulating genes associated with hypoxia-induced stress; it may also regulate apoptosis-related cytokines. In 2022, Xin et al used a low-pressure oxygen cabin mimicking 5,000 m altitude to evaluate whether pyroptosis is involved in the mechanism of retinal dysfunction in rat retinas. Hypobaric hypoxia significantly increased the expression of proinflammatory cytokines, including interleukin-1 beta and interleukin-18, indicating that pyroptosis is involved in the pathogenesis of HAR.

A recent study looked at the molecular mechanism of HAR. Su et al used an integrated bioinformatics analysis and a hypoxia-induced cell culture to identify genes FOS, IL10, IL7R, and seven different miRNAs as candidate biomarkers of HAR, which may help explain an individual’s increased susceptibility to this condition.
Global Perspectives

Assessment and Diagnostic Imaging

Patients with HAR usually have a history of ascent to a high-altitude location or even air travel with or without visual symptoms. Fundus photography may show an increase in the diameter of retinal vessels with tortuosity of arterioles and venules, along with diffuse dot-blot and flame-shaped hemorrhages, usually involving the midperiphery. Cotton-wool spots, Roth spots, vitreous hemorrhages, and papilledema may occasionally be seen as well.

OCT may detect a significant increase in retinal nerve fiber layer thickness in the temporal and nasal quadrants of the optic disc, along with an increase in the ganglion cell layer thickness in the superior macula. In one report, these changes were temporary and returned to baseline upon descent. Another study showed an increase in temporal and superior retina nerve fiber layer thickness following high-altitude exposure.

Fluorescein angiography may show bilateral leakage of retinal vessels peripherally, favoring venules more than arterioles, and optic disc staining. These findings resolve completely after descent to baseline altitude. The reduction in retinal function may also be detected by multifocal electroretinography, showing reduced responses in the macula that recover with time upon descent.

One case reported an increase in choroidal thickness (up to 530 μm) on OCT in a patient with HAR, suggesting that the hypoxia-induced increase in retinal blood flow could be associated with an increase in the choroidal blood flow and an increase in choroidal thickness. However, more studies are required to confirm choroidal changes in HAR.

Treatment and Prognosis

Although no evidence-based treatment exists for HAR and no active intervention is typically required, some reports suggest the use of steroids, nonsteroidal antiinflammatory drugs, diuretics, and supplemental oxygen, although without consistent evidence of effectiveness. Hyperbaric oxygen therapy has also been suggested.

The prognosis is favorable, with patients generally regaining their full vision in the weeks after descent. Visual impairment is rare, although it may occur in severe manifestations of HAR (eg, cilioretinal artery occlusion, central retinal vein occlusion). Recommendations for prevention include a slow ascent (no more than 300 m a day), allowing time for acclimatization, and immediate descent to baseline altitude if symptoms are progressing.

A Possible Sign of Trouble

Whether HAR is related to life-threatening conditions at high altitude is still a matter of debate. Clarke et al reported retinal hemorrhages as common findings due to the acclimatization process and denied their association with impending cerebral edema. Other findings suggest that vasogetic cerebral edema and altered autoregulation of the cerebral blood flow may correlate with AMS and HACE. Thus, early diagnosis may alert physicians to recommend immediate descent to avoid further progression of HAR or more serious, potentially fatal high-altitude illness.

Further studies are required to investigate the significance of HAR and whether it is a useful warning sign of potentially fatal conditions on the spectrum of high-altitude illnesses.

References:


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