Recommendations for traveling to altitude with neurological disorders

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ABSTRACT

BACKGROUND: Several neurological conditions might worsen with the exposure to high altitude (HA). The aim of this review was to summarize the available knowledge on the neurological HA illnesses and the risk for people with neurological disorders to attend HA locations.

METHODS: A search of literature was conducted for several neurological disorders in PubMed and other databases since 1970. The neurological conditions searched were migraine, different cerebrovascular disease, intracranial space occupying mass, multiple sclerosis, peripheral neuropathies, neuromuscular disorders, epileptic seizures, delirium, dementia, and Parkinson's disease (PD).

RESULTS: Attempts were made to classify the risk posed by each condition and to provide recommendations regarding medical evaluation and advice for or against traveling to altitude. Individual cases should be advised after careful examination and risk evaluation performed either in an outpatient mountain medicine service or by a physician with knowledge of HA risks. Preliminary diagnostic methods and anticipation of neurological complications are needed.

CONCLUSIONS: Our recommendations suggest *absolute* contraindications to HA exposure for the following neurological conditions: (1) Unstable conditions–such as recent strokes, (2) Diabetic neuropathy, (3) Transient ischemic attack in the last month, (4) Brain tumors, and 5. Neuromuscular disorders with a decrease of forced vital capacity >60%. We consider the following *relative* contraindications where decision has to be made case by case: (1) Epilepsy based on recurrence of seizure and stabilization with the therapy, (2) PD (± obstructive sleep apnea syndrome-OSAS), (3) Mild Cognitive Impairment (± OSAS), and (4) Patent foramen ovale and migraine have to be considered risk factors for acute mountain sickness.

KEYWORDS: acute mountain sickness, epilepsy, demyelinating disease, migraine, Parkinson's disease, high altitude neurological disorders

Introduction

There is an increasing interest in exploring location situated at high-altitude (HA) for leisure, sports (mountain climbing and alpinism), or work (astronauts, aviation, health care service, and alpine rescue) therefore, is not unusual to encounter people who develops acute symptoms related the HA exposure. The diverse extent of symptoms presentations is mainly due to the altitude reached and the ascending speed. During clinical practice, neurologists may also need to evaluate the risk or to advise people with pre-existing neurological disorders that are willing to going to HA areas.

The aim of this review is to summarize the available knowledge on (i) the neurological high-altitude illnesses (HAI), (ii) the risk of developing neurological symptoms at HA other than HAI, and (iii) the risk for people with neurological disorders to attend HA locations.

Physiological effects of low oxygen

Altitude is classified as low (500–2000 m), moderate (2000–3000 m), high (3000–5500 m), or extreme (>5500 m).[1] The main environmental modification with the altitude increase is the progressive reduction of the barometric pressure, being usually of 760 mmHg at sea level and around 523 mmHg at 3048 m above sea level. According to the barometric pressure decrease, also the atmospheric oxygen partial pressure (PO_2) decreases and remains always around 20.93% of the total barometric pressure (159 mmHg at sea level and 67 at 3048 m). Those modifications are termed hypobaric hypoxia (HH). The main human physiological consequence of going high is the reduction of the alveolar oxygen (O_2) which differs in acclimatized vs non-acclimatized individuals.

The acute exposure to HH induces alveolar hypoxia that causes the hypoxic pulmonary vasoconstriction to direct blood towards lungs areas better oxygenated. The hypoxemia activates

the arterial chemoreceptors (aortic and carotid bodies), whose fibers reach the nucleus tractus solitarius and the dorsal motor nucleus of the vagus nerve, increasing the alveolar ventilation to 1.65 times normal and with prolonged stayed up to 5 times normal. The increased ventilation determines transient hypocapnia and increase pH which in turns inhibit the bulbar (brainstem) respiratory center.

This response fades away in 2 to 5 days due to the metabolic gradual compensation induced by the kidneys with a gradual decrease in bicarbonate (compensatory metabolic acidosis). The bicarbonates are also reduced in the cerebrospinal fluid (CSF) and in the cerebral tissue thus decreasing the pH in the fluid around the chemosensitive neurons of the respiratory centers that are stimulated.[2] Hypoxia and hypocapnia have opposing effects on cerebral blood flow. Hypoxia increases CBF,[3-5] while hypocapnia decreases it.[5]

The hypoxemia stimulation of the chemoreceptor also induces cardioacceleration through an increased sympathetic activity that leads to an increase of heart rate, cardiac output and blood pressure.

Brain under hypoxia is protected till a critical threshold through different physiological mechanisms including the autoregulation and the increase of oxygen extraction which allows normal energy metabolism to be maintained. Autoregulation consists in vasodilatation (small pial vessels and large intra- and extracranial vessels) and reduction in cerebral vascular resistance during reduced cerebral perfusion to maintain the cerebral blood flow (CBF) constant or to increase CBF when also energy failure and/or a decrease in hemoglobin level are present.[6] However, acute hypoxia may induce functional changes such as an impaired cerebral autoregulation,[7] an increase of cerebral blood flow[8], and vascular permeability.[9]

The prolonged exposure to HA determines a gradual acclimatization mainly due to the increased erythrocytes' number (red blood cells) and hemoglobin concentration, increased pulmonary ventilation and diffusion capacity, increased angiogenesis in the peripheral tissue and increased cells O_2 utilization/extraction despite the low PO_2. Hypoxia also induces the production of the hypoxia-inducible factors (HIFs) which activate several genes encoding proteins necessary to ensure O_2 delivery for the tissue energy metabolism (genes related to endothelial growth factors and glycolytic enzyme, erythropoietin and mitochondrial genes, and genes that increase the production of nitric oxide).

The unique alveolar PO_2 measurement at 8400 m was performed by Grocott and colleagues[10] and they found a value of 43.1 mmHg with a barometric pressure of 253 mmHg.

Further maladaptive physiological brain effects have been shown in individuals after sojourns to HA.

Among structural changes there are white matter abnormalities,[11,12] reduced grey matter volume[13] and microbleeds due to hemosiderin deposit.[14]

Neurological manifestations related to the acute high altitude exposure: high altitude illnesses

Several factors are implicated in the appearance of neurological manifestations.

The rate of ascent, the altitude reached, the individual predisposition, and the physical effort along with others such as the temperature, the dehydration, the wind, and the exposure to solar radiation all may provoke typical neurological symptoms related to the HA exposure and overall defined as high HAI.[15]

The HAI include the HA headache (HAH), the acute mountain sickness (AMS), and the high altitude cerebral edema (HACE). The rapid ascent to HA in few people is the major determinant of the HAI. Several drugs are recommended to prevent or treat HAI,[16] and possible interaction of those drugs with preexisting neurological conditions and potential development of new neurological condition during exposure to HH are summarized in Table 1.

High altitude headache

The International Headache Society stated that >30% of the individuals that goes to high altitude (>2500 m) has HAH that typically develops in temporal relation to the ascent to HA and resolved within 24 hours after descent.[17] About 80% of lowlanders are susceptible to HAH at an altitude above 3000 m and almost 100% above 4500 m.[18] HAH is usually bilateral, of mild to moderate intensity, and it is aggravated by exertion, movement, straining, coughing, and/or bending. Risk factors include a history of migraine, low arterial oxygen saturation, high perceived degree of exertion, restrictions in venous outflow, and low fluid intake (<2 L in 24 hours). HAH usually subsides with analgesic (ibuprofen or paracetamol) hydration and avoiding further ascent, if those measures are not efficacious rapid descent should be advised.

Acute mountain sickness

The AMS can manifest in around 30-50% of the unacclimatized individuals that goes to HA (>2500 m), but in susceptible individuals even at lower altitude.[19] The incidence of AMS is higher for those that had a previous AMS and increases with the altitude, being less frequent below 2500 m (10-25%) and more frequent above 3000 m (up to 75%). Based on the recent consensus update, AMS manifests with nonspecific symptoms such as headache, which is the leading symptom required for the diagnosis, gastrointestinal symptoms (nausea or vomiting), fatigue/weakness, and dizziness/light-headedness whereas the sleep disturbances were removed from the previous score due to a repeatedly reported discordance of sleep from other AMS symptoms. AMS symptoms start to appear usually between 4 to 12 hours after arrival at HA. The presence of AMS is defined as a Lake Louise AMS Score ≥3 from the four rated symptoms.[19] The new LLS also gives the score related to the impact of AMS on overall function at HA (AMS Clinical Functional Score).

Table 1. Drugs used for prevention and treatment of high-altitude illnesses and interaction with drugs used in neurological conditions.

DRUGS	POSSIBLE SIDE EFFECTS AND INTERACTION
Acetazolamide (AMS, HACE prevention and AMS treatment)	Increased risk of salicylate toxicity in those taking Aspirin high dose (>300 mg/daily) Increased CBZ, PHT concentration Increased lithium excretion Possible increased suicidal risk in those on antiepileptic medications In association with several AEDs increased risk of osteomalacia Reduced serum and sodium potassium level Increased risk of metabolic acidosis and heat stroke in those on topiramate treatment Hyponatremia risk in association with duloxetine
Dexamethasone (AMS, HACE prevention and treatment)	Decreased Aspirin (or NSAIDs) level and can increase gastrointestinal symptoms: inflammation, bleeding, ulceration/perforation Decrease alprazolam concentration (induction of cytochrome P450) Altered behavior including state of agitation, euphoria, sleep disorders (restlessness and insomnia) Psychic effects: mania, psychosis, delirium, emotional lability and irritability, rarely altered consciousness and disorientation Drugs that induce cytochrome P450 3A4 reduce corticosteroid levels (phenytoin, carbamazepine, diphenylhydantoin, barbiturates) Enhanced coumarin anticoagulants (e.g., warfarin) activity May reduce the effect of anticholinergic drugs (trihexyphenidyl and biperiden) and cholinesterase inhibitors (rivastigmine, donepezil, and galantamine)
Nifedipine (HAPE prevention and treatment)	Increased metabolic clearance is induced by cytochrome inductors AEDs (PHT, CBZ, PB) while cytochrome inhibitors (VPA) and antidepressant (fluoxetine, nefazonode) increase the nifedipine concentration May trigger migraine crisis in migraine subjects with low threshold
Tadalafil/Sildenafil (HAPE prevention)	Caution in patients treated with CYP3A4 inductors (CBZ, PB, PHT, dexamethasone) since tadalafil plasmatic concentration can be reduced May induce headache
Salmeterol (HAPE prevention)	Caution in patients treated with CYP3A4 inductors (CBZ, PB, PHT, dexamethasone), CYP3A4 inhibitors (antidepressants) and with MAO-I (monoamine oxidase inhibitors) or TCA (tricyclic antidepressant) for cardiovascular side effects Can cause headache and tremor
Aspirin	Gastrointestinal ulcers associated with stress
Benzodiazepine	Sleep apneas and sleep disturbances Ocular and respiratory dysfunction in myasthenic patients Dependance can be given mainly by lorazepam in aged individuals
Ibuprofen And Paracetamol (AMS)	Increased gastrointestinal ulceration and bleeding risk if associated with corticosteroids, other NSAIDs (including COX-2 inhibitors) and SSRIs should be avoided PHT and lithium excretion is reduced Increase the anticoagulant effect (e.g., warfarin, heparin)

AEDs: antiepileptic drugs; AMS: acute mountain sickness; COX-2: cyclooxygenase-2; CBZ: carbamazepine; FANS: HACE: high altitude cerebral oedema; HAPE: high altitude pulmonary oedema; NSAIDs: non-steroidal anti-inflammatory drugs; PHT: phenytoin; PB: phenobarbital; SSRIs: Selective Serotonin Reuptake Inhibitors; VPA: valproic acid.

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Slow ascent, preacclimatisation and other pharmacological approaches to prevent, diagnose and treat AMS are discussed elsewhere.[16,20]

High-altitude cerebral edema

Leading neurological findings are truncal ataxia and altered mental status and in addition the presence of different other focal symptoms or psychiatric changes preceded or not by headache or AMS symptoms.[16] HACE represents a life-threatening form of acute HAI, that can be preceded by AMS or not,[21] and if this condition is not treated promptly it can result in death which can occur rapidly due to brain herniation.[22] Around 1-2% of individuals can develop severe symptoms compatible with the HACE that usually start between 24 to 72 hours after a gain in altitude. Immediate descent, oxygen, and dexamethasone administration are crucial. When rapid descent would not be possible due to the weather conditions, challenging terrain, or the presence of injuries or wounds, a portable hyperbaric chamber could be used if the

airway can be protected. An MRI study on 9 individuals with HACE showed, in 7 of them in the acute phase, T2 increased signal in the splenium of the corpus callosum that resolved in subsequent MRI study and all individuals had clinical recovery.[23] In patients survived from HACE, microbleeds were identified on susceptibility weighted images (SWI) in the cerebral white mater tracts.[9] This imaging data are related to vasogenic (extracellular) edema partly due to the breakdown of the blood brain barrier (BBB) and endothelial dysfunction. There are also reports of irreversible consequences of HACE, such as subcortical dementia and neuropsychiatric symptoms[24] and personality changes,[25] due to the hypoxia and the presence of lesions in the globus pallidus on MRI.

Neurological manifestations due to repetitive or chronic exposure to HA

Beyond these acute neurological manifestations, also *chronic* complications have been reported.

White matter hyperintensities

The white matter hyperintensities (WMHs) are nonspecific findings and commonly seen on MRI in normal aging with an increased prevalence with increasing age (10-20% at 60 years and near 100% above 90 years). WMHs are supposed to represent chronic small vessel cerebrovascular disease[26] and are also seen in association with different neurological conditions (e.g., migraine).[27] The presence of several risk factors may contribute to the progression of the WMHs in terms of volume and number and the progression over time is related to different neurological consequences (e.g., cognitive decline and gait abnormalities).

The presence of WMHs, observed on T2-weighted fluid-attenuated inversion recovery (FLAIR) images along with the diffuse reduction in WM integrity measured by diffusion tensor imaging (DTI), has been documented in extreme mountaineers who climbed over 4800 m,[23,28,29] in pilots[30] and in altitude chamber operations technicians[31] after repeated acute exposure to an altitude above 7260 m.[31] A retrospective study on 301 Tibetan patients residing at HA showed a high prevalence of WMHs and their presence was correlated with a younger age.[32] They also found an independent association of WMHs with several cardiovascular risk factors (e.g., hypertension, atrial fibrillation, and chronic cerebral infarction) but they failed to demonstrate an association with the hemoglobin level despite the higher levels present in Tibetans.

Chronic mountain sickness

The chronic mountain sickness (CMS) or Monge's disease[33] can develop in certain individuals that permanently live or are natives at HA (>2500 m). Worldwide there are around 140 million of individuals that live above 2500 m, of them 17 million live above 3500 m and 4 million above 4500 m and 5–10% are at risk to develop CMS.[34] The CMS prevalence depends on the altitude of residence and the population ethnicity since it has been demonstrated a different genetic adaptation to hypoxia in the different highlanders' populations. In the Andine HA residents, the CMS incidence and the erythrocytosis are increased[33] compared to Tibetan and Ethiopian. CSM is characterized by excessive erythrocytosis and severe hypoxemia which can lead to pulmonary hypertension and eventually congestive heart failure. Respiration is disordered during sleep, with episodic hypopnoea and apnoea. Individuals living at HA experience troublesome burning pain distally in the limbs.[35] The diagnosis is based on the presence of different symptoms such as headache; dizziness; breathlessness; and/or palpitations; sleep disturbances; fatigue; localized cyanosis; dysesthesia in the hands, palm, and foot soles; and reduced concentration and cognitive performance. CMS gradually disappeared with descent to lower altitudes.[36]

Test to predict acute mountain sickness susceptibility

A recent work describes the possible use of a hypoxia-test to detect subjects susceptible to severe HAI. With a decision algorithm based on a clinicophysiological score the physician with experience in high altitude medicine can advise on progressive acclimatization and prescription of drugs, such as acetazolamide, people who plan travel to altitude.[37] With the aid of this hypoxia submaximal exercise test the occurrence of severe HAI was reduced from 27% to 12% with correct recommendations. Other tests are present in literature with similar indications like a rest test both on the field or in simulate environment.[38]

Other neurological manifestations at HA and risks of exposure at HA for those with preexisting neurological conditions

Several neurological symptoms, in particular cerebrovascular accidents and seizures have been reported with high frequency at HA but their relationship with the HA exposure is not yet completely understood. The role of hypoxia is considered to be prominent.

In this section and the following paragraphs, we are going to discuss (i) different neurological conditions documented at HA that could present with or without any signs or symptoms of HAI and (ii) the possible worsening of the underlying disease in patients with preexisting neurological disorders when travelling to HA. Previous revision was done by Baumgartner et al[39] and Basnyat et al.[40] Therefore, we are going to update the current evidence and attempts are made to classify the risk posed by each condition and to provide recommendations regarding medical evaluation, advice for or against travelling to altitude, and effective prophylactic measures.[41] Unstable neurological disorders [e.g., brain tumor, recent transient ischemic attack (TIA), or stroke] are a contraindication for travel to HA due to a possible

worsening and a recovery impairment. In case of stable neurological conditions, the possible effect of exertion in addition to the hypoxia effect should be considered. Detailed anamnesis, neurological examination, and the presence of comorbidities should be carefully considered and case by case individually discuss to provide correct advice (e.g.,, passive or active ascent) in an outpatient mountain medicine service or by a physician with knowledge of travelling and HA risks. Development in diagnostic methods and treatment of neurological conditions are also mentioned. Based on the risk due to the pre-existence of neurological disorders, attempts will be made to provide recommendations to correctly advise for or against travelling to HA.

Literature and research methods

A search of the literature was conducted for several neurological disorders in PubMed and other databases. The studies were selected according to the following eligibility criteria: articles published before March 2021 and currently published journal articles. PubMed was used as the primary information source, but other databases were included in the search such as EMBASE, Web of Science, Cochrane Library to identify publication on HA exposure in patients with neurological disorders, with emphasis on clinical neurological series or individual cases reported at HA, from the early '70 to March 2021, without language restrictions. The following MeSH terms and/or keywords were used: high altitude, mountain travelling, hypoxia, neurological conditions searched were migraine and other types of headaches, transient ischemia of the brain, occlusive cerebral artery diseases, intracranial hemorrhage and vascular malformations, intracranial space occupying mass, multiple sclerosis, peripheral neuropathies, neuromuscular disorders, epileptic seizures, dementia and Parkinson's disease.

Cerebrovascular diseases

Stroke, hemorrhagic or ischemic, is defined as a relatively sudden occurrence of a focal neurological deficit.

Ischemic stroke. Ischemic stroke is usually due to the occlusion of a cerebral blood vessel that cause cerebral infarction. The occlusion could be due to atherosclerosis with superimposed thrombosis affecting large cerebral vessels, cerebral embolism, and occlusion of the small vessels. Hemodynamic stroke is a type of ischemic stroke that is caused by hypoperfusion. In other situation the ischemic damage is associated with other pathophysiological mechanisms: arterial dissection, inflammation (i.e., vasculitis), cerebral veins or dural sinuses thrombosis, hypercoagulable conditions, vasospasm and emboli of various origin (i.e., fat, cholesterol, and tumor). Ischemic stroke at HA have been reported and may be related with polycythemia, reduce plasma volume, dehydration, prothrombotic state, or impaired cerebral vascular autoregulation. Ischemic stroke could be also a complication of HACE.[42] The hematocrit and

hemoglobin levels increase with the altitude resulting in polycythemia which represents an independent risk factor for stroke.[43,44] Dehydration together with polycythemia contributes with consequent "inspissation sanguinis." Hypoxia may also determine endothelial dysfunction, coagulation abnormalities and platelet aggregation[45], and cardiac arrhythmias.[46]

Contradictory results have been reported in the literature on the relationship between *chronic* HA exposure and stroke possibly related to the heterogeneous ethnicity and different prevalence of specific cardiovascular risk factors, exposure to HA (transiently or since birth), and ethnic lifestyle habits (e.g., diet). The first report is from Sharma et al[47] in a small study of 13 stroke patients occurred after long stay (3 to 18 months at > 3000 m) and they observe in young patients an increased level of platelet adhesiveness. A higher prevalence of acute ischemic stroke (>anterior circulation) was reported in younger Tibetan (Tibet 3650 m) compared to Chinese lowlanders (Beijing 40 m) and the authors suggested that erythrocytosis and hyperhomocysteinemia possibly contribute to these differences.[48] Another retrospective study reported that the first-ever acute ischemic stroke in Tibetan plateau residents were more severe and showed a larger infarct volume and less artherosclerotic factors, suggesting a prevailing risk related to the hypercoagulable state due to polycythemia (reduced blood flow and increase peripheral resistance) and an increased hypoxia-inflammatory response at HA.[44] First ever ischemic stroke due to polycythemia induced by chronic HH (>4000 m) exposure have been reported in Indian soldiers more frequently at high compared to low altitude (13.7 vs 1.05/1000).[49] A study found an increased frequency of thrombotic stroke at HA in Saudi Arabia (Al Baha >2000 m vs Riyadh 620 m) probably due to increased hematocrit in conjunction with other factors (e.g.,, hypertension).[50] Another study suggests a higher incidence of stroke in Pakistani highlanders (>4500 m) compared to lowlanders (600 m).[51] Recently was published a case of stroke occurred in a 44-year-old experienced Sherpas climber who resides at HA (3800 m).[52] On the contrary, few epidemiological surveys conducted at different altitude suggested that cerebrovascular disease may be less frequent than at sea level. Razdan et al[53] performed the survey in the Kashmir region of South India (1530 m) among rural population. Cruz et al[54] performed a survey in Quiroga (Ecuador at 2300 m). Bancaleri et al[55] suggested a low stroke prevalence in Cerro de Pasco (Perù 4300 m). Kuller et al[56] reported a lower stroke rate at different HA locations compared to sea level in the United States. A lower incidence of stroke was found in a hospital in the Sub-Himalayan region India (Himachal Pradesh at 2200 m).[57] These discrepancies between studies may be due to other factors (e.g., others environmental stressor such as pollution in urban areas) and could be related to individual comorbidities in certain population. Furthermore, it has been suggested that HIF determines resistance against ischemia and improved cardiac function after ischemia.[44]

Several authors have reported ischemic stroke cases with the *acute* HA exposure in healthy subjects without any known risk factors (>4500 and 3600 m, respectively).[58,59] In the presence of deep vein thrombosis, a cryptogenic stroke due to a paradoxical embolism should be considered as a consequence of the increased pulmonary vascular resistance and arterial pressure due to the hypoxic vasoconstriction at HA which increased the likelihood of right to left shunting in those with a patent foramen ovale (30% healthy population). Indeed, embolic etiology was suspected in cases reported in the literature due to the presence of a large patent foramen ovale (3840 m).[60,61] Cases of deep venous thrombosis and associated pulmonary and cerebral embolism have been also reported, probably due to the increased prothrombotic state (4270 to 5790 m).[62,63]

Since dehydration, immobility or strenuous exercise may predispose to thrombosis it is recommended adequate hydration and exercise maintaining during altitude sojourn. Acclimatization is also essential to avoid HAI which may contribute to the reduced CBF. Recent data found that the risk of a second stroke or TIA after a minor stroke or TIA is 2.1% at 7 days, 2.8 at 30 days, 3.7% at 90 days, and 5.1% within 1 year.[64] A patient with previous TIA should be informed that the best treatment in case of recurrence is thrombolysis (when possible) and dedicated treatment in a stroke unit that may be difficult to be available in HA location or in adverse environment.

Cerebral venous thrombosis. The occlusion of cerebral venous sinuses and/or the tributaries cortical veins produces a venous ischemic stroke. Cerebral venous thrombosis (CVT) also cause raised intracranial pressure through decreased cerebrospinal fluid (CSF) absorption. The clinical presentation ranges from minor to life threatening depending on the site of venous occlusion (e.g., veins or sinus) and consequently the extent of brain parenchyma involvement and the effect of ICP. The clinical course is slower compared to the ischemic stroke, it is usually accompanied by headache and focal neurological deficit and complicated with seizures and hemorrhages and on neuroimaging are often visible multiple cerebral lesions not in arterial territories. Commonly affected sites are superior sagittal sinus (62%), transverse sinus (45%), sigmoid sinus (rare in isolation), and deep veins (internal cerebral veins, basal vein of Rosenthal, vein of Galen, and straight sinus). At HA all these sites involvement have been reported.[65,66]

Main risk factors at sea level are the hypercoagulable conditions (congenital or acquired thrombophilias) with thrombocytosis and hyperfibrinogenemia, head injury with direct venous trauma, estrogen-containing oral contraceptives, pregnancy and puerperium, infections, malignancy, and inflammatory disease. At HA other mechanisms include dehydration, hypoxia-induced hemostatic changes such as an increased platelet activity, volume depletion and secondary polycythemia, reduced mobility, inflammatory changes secondary to endothelial injury that accelerates the thrombotic process, hyperhomocysteinemia, exercise, and coagulation pattern triggered by

hypothermia.[67] These hemostatic changes do not appear during gradual ascent up to 45000 m,[68] therefore other mechanism may play a prevalent role such as the effect of the increased cerebral volume on CBF.[69]

CVT was reported in a necropsy of seven trekkers who died after HACE and/or HAPE while trekking in Himalayas.[22] The seven cases reported occurred after few days to few weeks of staying at an altitude range between 3440 and 6300 m asl. Cheng et al[70] reported a case of CVT with a poor neurological outcome occurred after 4 days at 4000 m without any known risk factors. Khattar et al[71] described 21 cases (2 died) of CVT; however, it is not specified the altitude and the length of stay at altitude; they observed a higher incidence of alcoholism (76%) in their retrospective cohort while a lower incidence of other comorbidities such as oral contraceptives (14%) and trauma (10%). Paliwal et al[65] described 4 cases (1 died) occurred at an altitude ranging from above 3000 to 3800 m asl without specifying the length of stay.

Other authors reported CVT cases occurred after several weeks of stay at HA. Song and colleagues[69] analyzed cerebral thrombosis at HA in their case and cases reported in the literature and they confirmed that all were mountaineers exposed for more than 3 weeks at HA (>5000 m) and all had cerebral thrombi of venous origin likely related to volume depletion and polycythemia.[69] Hassan et al[72] analyzed 28 cases of CVST occurred at an altitude >3000 feet but mostly (85.7%) > 8000 feet where they reside for >1 week; 27 had a good outcome and found overall a high level of hemoglobin and D-dimer and suggest that smoking and dehydration were the possible reversible risk factors in their cohort. Khan et al[73] reported a case of CVT due to deep cerebral vein thrombosis occurred in an otherwise healthy young man (20-year-old) after two weeks of stay at 4000 m asl.

Several authors reported CVT at extreme HA [>7200 towards Cho Oyu (8201 m), >5000 m towards Gasherbrum I (8068 m), Mount Everest at 8848 m and at 8511 m] with a length of stay ranging from 20 to 45 days.[66,74-76] Interestingly, while Khanal et al[66] reported the involvement of the right transverse and sigmoid sinus in a subject with low protein S plasma activity, all the other authors reported the involvement of the superior sagittal sinus in subjects without any known risk factors.[74-76] Familial thrombophilia (protein S or C deficiency, heterozygous Factor V Leiden mutation) was identified as the cause of few CVT case reports occurred between 3000 and 8848 m asl.[66,77-79]

A case of CVT in a young woman working in a high-altitude chamber as instructor have been reported and mostly related to the oral contraceptive assumption.[80]

CVT is a challenging condition due to its wide range of clinical presentations. The persistence of headache and focal neurological symptoms after descent suggests to always evaluates the possibility of CVT, especially in those predispose (e.g., due to thrombophilia), including a magnetic resonance venography to the neuroimaging stroke workup. The presence of

multiple hemorrhagic infarctions in one hemisphere without atherothrombosis or embolism source suggest a cortical vein origin. Careful history and medical screening should be performed individually before going to altitude. There are no evidence-based guidelines to make firm recommendations; however, it should be considered to advise all travelers to HA to drink adequately (2-3 L of water/day) to avoid dehydration and hyperviscosity, avoid strenuous activity at high summit and those with known predisposing factors to thrombosis to avoid altitude sickness (e.g., HACE and the increased ICP which further compromise the CBF) considering all the measures that are helpful (e.g., acclimatization and specific treatment). In addition, women on oral contraceptives should consider the risk of being exposed to HA.

Reversible cerebral vasoconstriction syndrome. Reversible cerebral vasoconstriction syndrome (RCVS) is characterized clinically by severe headache (hyperacute and excruciating) with or without fluctuating neurological symptoms (TIA-like episodes) or seizures associated with reversible vasoconstriction of the medium and large cerebral vessels.[81] Known risk factors are eclampsia, peripartum period, the use of vasoactive substances (including triptans and selective serotonin reuptake inhibitors), and strenuous exercise but also an idiopathic variety exist. The suggested mechanism is a transient disturbance in the control of cerebral sympathetic vascular tone.[81] Recently two cases were reported of RCVS developed acutely at HA suggesting that also altitude may provoke it (1200 and 3650 m).[82,83] Therefore, this condition should be considered in the differential diagnosis, given its reversibility when the main cause is revealed and adequately treated. Although the pathophysiology is still poorly understood it may be useful to recommend avoiding at HA adjunctive possible risk factors such as all vasoactive substances (e.g., nasal decongestants, selective serotonin reuptake inhibitors, or SSRI).

Posterior reversible encephalopathy syndrome. There is an acute increased perfusion and blood pressure (BP) increase after few hours at altitude which remains higher during HA sojourn and further increased with the increased altitude as demonstrated in the HIGHCARE-Himalaya study.[84] Due to the elevated hypoxic peripheral and central chemoreflex sensitivity,[85,86] hypertensive individuals may be more susceptible to HA deleterious effects.

Hypertensive encephalopathy can develop in such individuals presenting with headache, seizures or focal neurological signs and edema in the subcortical white matter which is usually reversible although hemorrhage or infarction may occur.

Posterior reversible encephalopathy syndrome (PRES) presents with severe headache, nausea, or vomiting, with or without neurological symptoms mainly referable to the parietal and occipital lobes (e.g., visual field deficits, hallucinations, confusion sometimes leading to seizure and coma) due to severe hypertension (diastolic pressure >125 mmHg).[87] The clinical

presentations are variable depending on the underline etiology. A multifocal vasoconstriction of the cerebral arteries is implied and typically resolves in 1 to 3 months. The hypertension leads to cerebral autoregulatory failure and vasodilation with interstitial fluid extravasation and vasogenic edema[88] with a predilection for the posterior circulation thought to be related to the lack of sympathetic activity.[89] When promptly recognized and treated, the symptoms and radiological abnormalities can be completely reversed, otherwise the symptoms progress to ischemia with large infarction and death. Given its reversible nature when promptly recognized, it is of a paramount importance to consider it in the differential diagnosis including a magnetic resonance angiography in the neuroimaging workup.

Hemorrhagic stroke. The hemorrhage occurs within the brain parenchyma (i.e., intracerebral hemorrhage) or within the subarachnoid space and ventricular system (also termed subarachnoid hemorrhage). The main cause of intracranial hemorrhage is considered the arterial hypertension that may worsen at HA due to cardiovascular response to HA[90] but in patients with amyloid angiopathy there is the risk of high recurrence of lobar hemorrhage even at sea level and therefore these patients should not be recommended to ascent to HA. In case of recent acute neurological events patients should not ascend to HA. In case of previous hemorrhages, the situations need to be carefully evaluated considering comorbidities and stable conditions.

There are few data on the frequency of cerebral intracranial hemorrhage at HA. Intracranial hemorrhage is the most frequent stroke subtype reported on the Tibetan plateau in China (74.1%).[91] A prospective hospital-based study investigated the main cause of intracranial hemorrhage (ICH) and outcomes in Tibetans and found that most of the cases are caused by hypertension and that those patients are at greater risk of disability or disability/death on follow-up compared with patients from the area of Chengdu located at low altitude.[92] A nontraumatic subdural hematoma case has been reported following acute HA exposure.[93]

Subarachnoid hemorrhage. At HA there is an increasing blood flow and augmented capillary permeability related to the brain adaptation to HA. The adjunctive role of the decreased barometric pressure may increase the aneurysm or arteriovenous malformations rupture event.

Subarachnoid hemorrhage (SAH) is usually related to an aneurysm rupture due to increased pressure which force the blood into the subarachnoid space. Aneurysm of 10 mm or more of diameter are more susceptible to rupture being the likelihood of rupture those smaller than 10 mm between .05% and .7% per year.[94,95] Risk factors includes hypertension, physical activity (e.g., sexual activity), straining at stool or during natural delivery, sometimes even due to coughing or sneezing. The leading symptoms is the headache usually refers by the patients as the "worse ever had" and various degree of altered mental status which make the differentiation with HACE difficult. SAH

were reported in a necropsy of seven trekkers died after HACE and/or HAPE while trekking in Himalayas.[22] The bleeding risk of aneurysm, arteriovenous malformations and cavernous hemangiomas at HA is not yet determined. A case report of bleeding from a middle cerebral artery aneurysm has been reported in an acclimatized man who develops suddenly severe occipital headache and after 1 hour loss of consciousness upon descent (from 4700 to 4200 m) and subsequent gradual (over days) progression of neurological symptoms.[96] Two cases were reported of SAH due to a small (4 mm diameter) aneurysm rupture, one developed in a man during air travel landing[97] and the other developed both before and after landing.[98]

Recommendations for patients with history of recent/past ischemic and hemorrhagic stroke or transient ischemic attacks

For patients with a recent stroke (less than 90 days) data are lacking regarding the safety of trekking to HA therefore it is not recommended to go to mountain. For patients with previous stroke several aspects are worth considering: (i) the definite diagnosis based on clinical history and neuroimaging, (ii) a stable control of risks factors (arterial hypertension, hyper-colestherolemia, hyperglycemia, metabolic syndrome, anticoagulants for atrial fibrillation, smoking habits).

Further, (iii) in those with atherothrombotic stroke it is recommended a carotid ultrasound within the previous 6 months, to prevent the risk of HA complications in a plaque or a severe stenosis, (iv) for those with cardioembolic stroke a cardiological evaluation with echocardiography it is recommended and novel oral anticoagulants in those with non-valvular atrial fibrillation are preferable to warfarin in a remote environment, (v) in those with a cryptogenic stroke further evaluations including coagulation abnormalities study or patent foramen ovale exclusion are needed.

TIA is often a clinical diagnosis which suggests that such patients should not trek or climb at HA alone. It is important to consider that loss of consciousness, dizziness, falls, amnesic or confusional episodes as isolated symptoms are not necessarily TIA.

Arterial hypertension is the main cause of hemorrhagic stroke and HA increases blood pressure leading to adverse effects on cerebral aneurisms and arterial venous malformations. Patients with amyloid angiopathy are at risk of lobar hemorrhage, therefore patients with such conditions are advised to avoid altitude. A moderate or severe disability post-stroke measured with the Rankin scale (>2) is a contraindication to visit a wild environment. It is advisable to encourage patients with previous stroke (but this applies to most neurological patients) to avoid trekking alone.

Syncope

The occasional occurrence of syncope is reported over 3000 m in non-acclimatized persons, this is in relation to vasovagal stimulation, and we will only mention that some cases might be susceptible to drug treatment. Nicholas et al[99] reported 94 cases seen in healthy young adults in an emergency room over 12-month in Colorado (3293 m) that mainly occurred in the first 24 hours of HA reached and they named it *high-altitude syncope (HAS)*. HAS is usually benign and differently from a seizure the patient usually shows a rapid recovery with no prolonged confusion or disorientation. Freitas et al[100] reported a case of a young women with repeated syncope while climbing at HA (>2000 m) confirmed to be of neuro-cardiogenic origin (positive 70° head-up tilt test) and successfully treated with beta blockers (atenolol 50 mg).

Acute hypoxia exposure induced increased sympathetic activity that increased cardiac output to maintain arterial oxygen content. The sympathetic vascular tone control and baroreceptors responsiveness are suggested mechanisms underlying neurogenic syncope. Indeed, an increased sympathetic activity prior to syncope has been shown using microneurography and heart rate variability studies and this activity ceased at syncope onset.[101] Moreover, vascular resistance is reduced prior to syncope which is thought to be due to the initial adrenergic discharge that at high levels cause vasodilatation in intramuscular blood vessels. Prolonged sympathetic activation induces downregulation of beta-adrenergic receptors as shown during exercise in chronic hypoxia.[102]

Transient global amnesia

Transient global amnesia (TGA) is a syndrome characterized by memory loss (e.g., anterograde memory) and confusion/disorientation lasting from 30 minutes up to 24 hours.[103] Four TGA cases related to HA have been described in the literature (altitude range between 2000 and 5500 m; length of stay at altitude range between 1 to 10 days), enough to deserve the definition of HA global amnesia.[103-105] TGA is often triggered by the effort and sometimes associated with emotional factors. Hypoxia could play an adjunctive etiological role, predominantly affecting memory circuits (Papez circuit), and further aggravate by the hypocapnia resulting from the hypoxic ventilatory response (HVR) that induces cerebral vasoconstriction.[105] TGA occurs frequently on the first or the second day of vacation and it has been found to be associated with high blood pressure levels. Those patients can be examined in hospitals located near ski resorts or mountain huts. In the differential diagnosis, an untested head injury or an acute cerebrovascular event should be considered if the memory deficit does not regress and focal signs are present. Prognosis is benign as in cases occurring at low altitudes and relapses are rare. An association with patent foramen ovale has been described. A previous and unique TGA is not a contraindication for altitude travel or flying. In case of recurrence a specific advice is needed by an expert physician.

Migraine

In the general population, migraine is a widespread disease, with a prevalence of about 12%, which can reach 22-25% in women

of childbearing age. HH is certainly a trigger for migraine attacks.[106] Some epidemiological data suggest an increased prevalence of migraine in HA populations[107] but also a worsening of both frequency and intensity of migraine episodes in low altitude residents during trekking or long flights.[108] There seems to be no difference between migraine without (M) or with aura (MA). M does not present an increased risk of developing cerebrovascular events, while in MA this risk is significantly increased even in young people with associated risk factors, such as smoking and oral contraceptive therapy.

During a mountain medicine consultation, it is common to evaluate people with migraine who ask advice for traveling at HA or who have already experienced a worsening of their headache. It is not easy to distinguish between HAH also associated with AMS and migraine crises,[109] therefore a neurologist with specific experience is needed. The presence of additional symptoms in AMS may help since the Lake Louise score define AMS as the presence of headache plus one or more adjunctive symptoms (anorexia, nausea/vomiting, fatigue, dizziness/vertigo) in an unacclimatized person who rapidly ascend >2500 m. Headache is usually bilateral and described as stabbing or dull pain whereas migraine typically is unilateral and describes as throbbing or pulsing pain. Since migraine can worsen at HA, patients with an increase and high frequency of migraine attacks particularly those with MA should be referred to a specialist before planning to visit HA locations. When migraine patients plan to do a trekking, expedition or even a long HA trip, they must have an adequate amount of symptomatic and prophylactic drugs in the bag. The use of triptans seems to be safe.[110] One study suggested some usefulness of triptans in AMS prevention.[111] However, a recent Cochrane review degraded the evidence of the latter study due to low quality and imprecision.[112] Acetazolamide can also be effective in migraine prevention. Patients with MA should adequately check and control vascular risk factors (e.g., thrombophilic state) and stop smoking. Estrogen is an absolute contraindication, even at low altitudes. In patients with migraine and *atypical* aura (multiple aura symptoms: visual, sensory, speech and/or language, motor, or autonomic) prolonged over several hours to 3 days) especially if it is the first attack and after age 40 and predominantly negative symptoms (e.g., hemianopia), a brain MRI with DWI study should be performed before travel to disclose recent embolic subclinical strokes. In addition, a transcranial Doppler to disclose a patent foramen ovale (PFO) or the presence of a right to left shunt should be also preventively performed even though there are no data on the efficacy of the closure of PFO in the prevention of stroke at high altitudes in those patients. A small study suggests that PFO is a possible risk factor for HAPE.[113]

Delirium and high altitude psychosis

Delirium is an acute modification of cerebral function in response to stressors (e.g., acute illnesses, drug, or alcohol intoxication) and develops over a short time (hours to days). Delirium manifests with confusion and reduced concentration, insomnia, overactivity, tremor, vivid hallucinations, and sometimes excessive sympathetic activity (flushed face, dilated pupils, injected conjunctivae, rapid pulse and blood pressure rise, increased sweating). Delirium can be induced by hypoxia[114] but other causes related to HA have been suggested to be implicated, the hypocapnia-induced vasoconstriction and alkalosis.[115]

Delirium in mountain climbers may appear as described in several cases reported in the literature (altitude >7000 m).[116]

Hallucinations and other psychotic symptoms may appear at HA with or without other symptoms of delirium or HACE.[117] Isolated HA psychosis in climbers have been reported (e.g., the "third man" phenomenon) at an average altitude 7280 m and to disappear upon descent, but it is associated with an increased risk of accidents.[117] If rapid descent is not possible antipsychotic should be given or cognitive strategies (e.g.,, reality testing) can be adopted by the affected climbers or by a partner.[118] Organic causes need to be rapidly excluded.

Depression, anxiety, and insomnia

The presence of depression is either pre-existent or caused by HA exposure and according to Hüfner et al[119] physical activity at HA might be beneficial. In expedition, travelling, and HA exposure, there should be a strategy to avoid mood disorders, that might be due to altered neurochemical status, including neuro-encephalins, or altered blood-brain barrier.

Depressed individuals going to HA with a pre-existing psychiatric condition should be in a state of stable disease with no recent change in medication. There are, however, cases in which a latent depression might be revealed by isolation and HA. Such cases should have psychotherapy and encouraged to descend, especially because drug treatment at HA is poor, since most benzodiazepine are contraindicated at HA, similarly to alcohol use. The only tolerated hypnotic is Zolpidem 10 mg.

Another important notion is that there is an interaction between altitude and drug use. For instance, about one third of people with stroke have occult depression and several are on antidepressants, but a relative serotonin depletion due to hypoxia could be associated with resistance to standard antidepressants. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants, and this should be considered in post-stroke depressed patients.

Boos et al[120] in a Nepal trekking investigated the relationship between anxiety and AMS, this study involved 80 participants over 10 consecutive altitudes up to 5140 m during a trek. The majority of previous studies tended to be smaller and assessed only 1 or 2 altitudes. Furthermore, the subjects in this study[120] underwent an identical ascent protocol, staggered by 2 days. They included much higher altitudes than most studies done, which strengthened the relationship between anxiety and AMS given by the Lake Louise Score. HA anxiety symptoms may be

difficult to be distinguished from AMS symptoms thus as suggested travelers should be advised about the symptom's similarity between the two conditions.[119]

Sleep alteration and its relationship with periodic breathing are altitude-related, the discussed hypocapnia suppresses ventilatory drive to the point of apnea. Carbon dioxide levels increase, stimulating respiration, which (with hypoxia) produces hyperventilation, and the cycle repeats, producing periodic breathing. Respiratory control involves both central and peripheral mechanisms.

Sleep architecture becomes progressively more disturbed and periodic breathing more frequent, while REM sleep is preserved. Both dreams and nightmares might, however, contribute to psychic homeostasis and be useful in stressing environments. Johnson et al[121] in a Nepal trekking observed increasing episodes of apnea/hypopnea (AHI) and higher arousal index (AI) from Kathmandu (1500 m) to Lobuche (5000 m).

Although not specifically studied in patients with obstructive sleep apnoea syndrome (OSAS) at HA, the addition of low flow (1-2 L/min) nocturnal oxygen is helpful in climbers and may be advantageous in patients with OSAS to reduce both periodic breathing and central apneas. Given the high prevalence of psychiatric condition in general population is not uncommon that such pre-morbidities may be present in climbers or travelers to HA.[119] We recommend maintaining current medication, avoid drugs interaction, alcohol, and hypnotic drugs assumption.

Cranial nerve palsies

Several cranial nerves palsy have been reported at HA due to different causes such as hypoxia induced brain swelling and increased intracranial pressure, barometric pressure changes, dehydration and possibly vasospasm or a hypercoagulable state, cold or infections. Beyond the well-recognized sixth cranial nerve palsies due to cerebral swelling at HA, in most of the reported cases due to other etiology a complete recovery has been reported after several weeks or months. Unusual cases of acute unilateral optic neuropathy secondary to barotrauma following a medial orbital wall fracture has been reported[122] as well as an anterior ischemic optic neuropathy in pilots[123] and secondary to decompression sickness.[124,125] Oculomotor nerve palsy (III cranial nerve) has been reported (3600 m).[126] Abducens nerve palsy was found at HA both isolated and correlated with HACE (in less than 1%)[21,22] and possible mechanism are HA increased intracranial pressure, brain edema, vascular lesions, or stress induce latent amblyopia.[40,127,128] Facial baroparesis (VII cranial nerve palsy), typically due to the increased pressure compressing the nerve in the middle ear cavity, has been reported in 11 published case report due to HA air travel or mountain trekking (4300 m reached in 6 days).[129,130] Hypoglossal nerve palsy probably due to increased pressure in the hypoglossal foramen has been reported (3500 m reached from 2500 in 3 days).[129]

Neurodegenerative disorders

Multiple sclerosis. Multiple sclerosis (MS) is an autoimmune disease and repetitive proinflammatory cascades could also act at the endothelial level causing decreased vasodilatory capacity reducing the neurovascular coupling during task execution. This cerebral vasoreactivity (CVR) impairment together with the hypoxia related damage occurring in acute inflammatory lesions,[131] suggests that patients with MS must be advised to avoid altitude to prevent a possible new relapse, even when symptoms are mild. The possible involvement of the autonomic nervous system in patients with MS may also be related with the lack of compensatory mechanism with the exposure to altitude. An exacerbation of a relapsing remitting MS was recently reported with acute exposure to HA (Mt. Fuji at 12388 feet/ 3776 m).[132] A high AMS occurrence (after 48 hours at altitude and symptoms lasting 2 days) has been reported in MS athletes at HA during the National Veterans Winter Sports Clinic in Snowmass, Colorado (2470-3813 m).[133] Another study has found that athletes with neurological impairments (including MS) with a prior history of AMS and headache at HA have a higher Lake Louise Score (LLS).[134] Nine MS patients participated to a 5-day expedition to Machu Picchu and most of them experienced altitude sickness >3600 m or more and were treated with analgesic if needed, they also reported transient sensory complaints and increased equilibrium disturbances but without evidence for any relapses.[135]

Beyond hypobaric hypoxia (HH), other environmental stressors such as temperature (T) may affect negatively MS patients. MS patients may develop new neurological signs and symptoms if they present an infection or if exposed to cold (e.g., central pain exacerbations due to cold hypersensitivity).[136] A high prevalence and mortality rate of MS patients have been reported in US high-altitude states with average low temperatures (CO, WY, and MT).[137] The detrimental effect of elevated environmental heat has also been reported since long time. Indeed, in the past the diagnosis of MS was performed using a hot bath test which induce temporary symptoms (e.g., visual impairment, fatigue, motor disability or tingling) the so called "Uthoff's phenomenon." Therefore, MS patients are particularly sensitive to high outdoor temperatures and humidity which can raise the core T, and exercises-induced hyperthermia even after short-term exposures. However, the possible long-term adaption may improve thermoregulation of MS patients in the high-temperature and low-latitude region and explain the higher prevalence and mortality rate in colder and higher states reported.[137] Furthermore, a decreased risk of MS has been reported after exposure to ultraviolet radiation.[138]

In conclusion, the exposure either acute or chronic to HA does not seem advisable and a personalized evaluation should be

performed before the clinicians can advise properly patients with MS to whether or not they could go to HA.

Mild cognitive impairment and dementia. Mild cognitive impairment (MCI) is a condition in which individuals demonstrate minimal cognitive impairment of instrumental activities of daily living and it is considered to be an intermediate state between normal cognitive aging and early dementia.[139] However, the progression toward dementia may reverse as it has been showed in approximately 24% of the individuals in different longitudinal studies.[140] Several factors (e.g., lifestyle) have been implicated in MCI reversion. The possible contribution of hypoxia in the progression of the MCI into dementia is not yet established. Hypoxemia is a crucial factor for cognitive impairment in patients with pulmonary (e.g., COPD)[141,142] and cardiopulmonary disorders,[143,144] and the degree of cognitive impairments is closely related to the degree of hypoxia. In patients with cardiac arrest have been found that hypoxia increase β-amyloid (Aβ) level.[145] In an animal model has been found that chronic HA exposure induces learning and memory deficits and the reduced expression of several synaptic proteins and astroglial cell markers in different brain areas.[146] Recent studies suggest a potential beneficial role of limited exposure to hypoxia. Experimental intermittent hypoxia (IH)-hyperoxia training has demonstrated improvement in cognitive functions and decreased Alzheimer's disease (AD) biomarker in MCI patients.[147]

Well-adapted elderly Andean HA dwellers compared to lowlanders showed a slightly impaired cognitive function.[148-150] Higher MCI prevalence was found in 1000 lowlanders staying at HA (>4300 m) for >12 months in India compared to 1000 lowlanders staying at sea level.[151] On the contrary, a cognitive screen performed in 481 HA (2100 m-4000 m asl) residents in developing regions (aged >60 years), 1.37% were classified as MCI whereas the 98.8% of the subjects scored within normal range.[152] The contradictory results may depend in the latter case on specific population characteristics (e.g., illiterate), but could also be related with the reduced environmental and cardiovascular risk factors in rural population.[152] Several studies have investigated the acute and chronic effect of HA exposure on cognition in healthy subjects, and it is still not clear whether there is a selective or a general impairment of tasks investigating both central executive (working memory set-shifting, updating, monitoring, inhibition, and planning) and non-executive (perception, attention, and short term memory) functions.[153-155] Two cases of secondary subcortical dementia with neuropsychiatric symptoms, due to lesion in the globus pallidus bilaterally, following HACE at HA (3500 m) have been reported.[24] Due to the potential deleterious effect exerts by hypoxia on cognitive functions it is not advisable to allow patients with any type of dementia to go to altitude and this could be applied also to MCI patients. Moreover, the use of dexamethasone in case of HAI can reduce the effect of

anticholinergic and cholinesterase inhibitors drugs therefore worsening the cognitive symptomology.

Parkinson's disease. PD is related to the neurodegeneration of the nigrostriatal dopamine system that lead to a decrease dopaminergic transmission in the basal ganglia (BG). BG are particularly susceptible to hypoxia-ischemia due to their high metabolic activity.[156] There is evidence that OSAS due to chronic intermittent hypoxia contributes to the pathogenesis of PD increasing the alfa-synuclein levels.[157] Severe and prolonged hypoxia contributes to brain damage, but moderate hypoxia exerts a neuroprotective effect through HIF-1alfa activation in PD model[158] while low level of HIF-1alfa is associated with neuronal dopaminergic cell loss in the substantia nigra pars compacta (SNpc) and contributes to PD pathogenesis.[159] HIF1alfa pathway is proposed as a therapeutic target for PD.[160]

The possible involvement of the autonomic nervous system in patients with PD may lead to the lack of compensatory mechanism with the exposure to altitude. In PD patients has been reported an impaired chemosensitivity to hypoxia and perception of dyspnoea.[161] Dyspnea is frequently reported by 40% of PD patients,[162] enough to deserve to be included in the clinical evaluation screening thorough the nonmotor symptoms scale (NMS) and in the evaluation of their impact on daily life part I of the Movement Disorder Society—Unified PD Rating Scale (MDS-UPDRS) as it has been suggested.[163] One case of Parkinsonism after acute HH exposure (up to 16000 ft-4876.8 m) resulting in damage of the basal ganglia has been reported.[164] However, there are no published data in the literature regarding patients with idiopathic PD traveling to altitude. Few studies were performed to evaluate the effects of mountain exercise in PD's patients and demonstrate improvement in motor performance and social cognition; however, it is not specified at which altitude they stayed.[165,166]

Screening for OSAS or dyspnea should be included in the evaluation of PD patients willing to travel to HA location and if positive they should travel with non-invasive ventilatory support. Due to the fluctuation of nonmotor symptoms (e.g., dyspnea) and motor symptoms in advanced PD patients, mainly related to the response to the dopaminergic medications, every patient should have specific oral antiparkinsonian drugs promptly available, should always visit the mountain accompanied and maintain adequate hydration. In conclusion, a careful personalized evaluation should be made by a neurologist expert in the field considering other risk factors such as prior history of any HAI.

Tumors

Neurological symptoms presenting at HA may be related to HAI and usually ameliorate or resolve to a certain extent upon descent, whereas the persistence of them suggests the presence of intracranial lesions.

Three cases were reported of brain tumors both malignant and benign which suddenly become symptomatic when people are exposed to HA (range between 3000 and 4000 m).[167,168] A similar problem is presented by arachnoidal cysts and pinealomas.[167] This might be due to edema, an increase in cerebral blood flow, or increased cerebrospinal fluid pressure. Patients with brain tumor (e.g., colloid cyst) may have obstructive hydrocephalus which can worsen with the pressure changes due to HA. These events are usually well-tolerated in healthy individuals but may lead to severe consequences in patients with brain lesions, given the lack of brain reserve. Following craniotomy have been documented residual trapped air that expand at HA[169] and cause raised ICP leading to severe neurological symptoms depending on the underlying cause.[170] Patients with known intracranial lesions are unstable and should not travel to HA.

Brain trauma and other lesions

HA exposure slow the brain repair resulting from a concussion.[171] Management of brain trauma aimed to prevent a further or secondary brain insult minimizing the occurrence of hypotension and hypoxia.[172] In addition, hypobaria exerts a negative effect on intracranial pressure and cerebral perfusion pressure. There are evidence suggesting an increased blood-brain barrier permeability enhancing action of free radicals is also possible. In highlanders, residents mortality and nerve function recovery after a traumatic brain injury and decompressive craniotomy were affected by the elevated hemoglobin concentration due the chronic HA exposure.[173]

For a patient with a traumatic or metabolic brain injury, such as CO poisoning, severe previous COVID-19 infection, previous brain hypoxia or after a cardiovascular operation[84] it does not seem advisable to go at high altitude.

Peripheral nerve disorders and neuromuscular disease

Diabetic neuropathy is frequent while other condition affecting peripheral nerves or neuromuscular disorders are unfrequent. Inherited or acquired sensory motor peripheral neuropathies reduce the sensibility of the foot, during walking or climbing causing risks. Beside hyperglycemic episodes in diabetic neuropathy there are in addition microvascular abnormality, segmental demyelination and remyelination. This angiopathy is further aggravated by the exposure to hypoxia, therefore microtraumatic events and/or cold exposure could aggravate these angiopathy and induce nerve demyelination or axonal atrophy. Neuropathic patients should be advised to wear comfortable shoes, accounting for the individuals' feet shape and possible deformities, but also for the feet sizes' variability due to prolonged standing position, to avoid further reduced blood flow to the extremities.

The present recommendations are that hydration should be maintained, immobility should be avoided or flight socks when flying encouraged to prevent deep venous thrombosis and wearing warm comfortable stockings during mountaineering activities. There is no evidence that previous peripheral damage can progress at altitude. Paulson et al[174] found that Charcot Marie Tooth patients were at risk of developing dysarthria, incoordination and difficulty walking after returning from skiing at 8000 ft in the Colorado mountains.

Neuromuscular disorders such as muscular dystrophies, myotonic dystrophy, and amyotrophic lateral sclerosis, can facilitate alveolar hypoventilation provoking hypoxemia and sleep disturbances, including sleep apnea, with nocturnal hypoxemia to an oxygen saturations level as low as 75% at sea level. At altitude these patients can have higher desaturations risks. Therefore, patients with neuromuscular disorders should be screened for the presence of sleep apnea prior to travel to HA and, if sleep disturbance is detected, they should travel with non-invasive ventilatory support.[175] Patients with neuromuscular disorders with a decrease of forced vital capacity (FVC) of >60% should not travel at medium/high altitude.

Further research and insight for muscle mass loss and the understanding of the muscle protein pathways could further provide recovery for HH effect. Ruggiero et al[176] showed that acute exposure to severe hypoxia exacerbates peripheral fatigue and muscle slowing compared with sea level, that only appropriate acclimatization to HA reversed the effects of acute hypoxia, at least in those not on medication.

Cramps might be a sign of muscle fatigue but also a sign of occult or known peripheral neuropathy.

Myoglobinuria might be due to poor hydration or electrolyte unbalance.

Rhabdomyolysis is a definite risk for travelers due to unaccustomed physical exercise, other factors contributing to the risk of myoglobinuria are beside inadequate preventive hydration, high ambient temperatures, supplement use (e.g., creatinine and herbal weight loss supplements), or certain medications (e.g., statins, selective serotonin reuptake inhibitors), illicit drug or alcohol use, or recent viral illnesses. The first step when encountering rhabdomyolysis after strenuous exercise is to determine whether the rhabdomyolysis is clinically significant, requiring descent or intravenous fluid administration. Since corticosteroids might transitory increase glycemia and cause hypokalemia caution should be paid in treating acute HA illnesses (e.g., HACE, HAPE) to avoid in diabetic travelers the ketoacidosis. Since also acetazolamide can induce ketoacidosis, it should never be used in diabetic patients. Caution should be exert with the use of both corticosteroids and calcio-antagonists due to their metabolic and vasoactive effect. GABAergic medication used for neuropathic pain should be reduced to avoid drugs interaction in case of emergency drug treatments.

Epilepsy/seizure at high-altitude

Seizures at HA may occur in the setting of AMS or HACE,[177] but can be also elicited by the HA exposure in persons with

Table 2. Adaptive and maladaptive altitude responses and neurological consequences.

ADAPTIVE MECHANISMS	MALADAPTIVE CONDITIONS	POSSIBLE NEUROLOGICAL CONSEQUENCES
Hypercoagulable state (e.g., polycythemia, platelet aggregation, coagulation abnormalities)	Increased hypoxia-inflammatory response (endothelial dysfunction)	Ischemic stroke Cerebral venous thrombosis
Reduced plasma volume	Dehydration Cardiac arrhythmias	
Cerebrovascular autoregulation	Impaired cerebrovascular autoregulation	Ischemic stroke RCVS Possible MS relapses
Hypoxic pulmonary vasoconstriction	+ PFO and deep vein thrombosis: paradoxical embolism	Cryptogenic stroke
Hypoxic peripheral and central chemoreflex sensitivity	Increased blood pressure	PRES Hemorrhagic stroke
Vasodilation	Increased capillary permeability and blood flow in the brain	+ Decreased barometric pressure in the presence of aneurisms--> subarachnoid hemorrhage
Hypoxia induces increased sympathetic activity	Exaggerated sympathetic activity	Syncope
Hypocapnia and hypoxic ventilatory response	Cerebral vasoconstriction	TGA Delirium
Increased CBF	Activation of trigeminovascular system	Migraine
Periodic breathing	Central apneas	Sleep alterations
Hypoxemia	1) Increased β-amyloid (Aβ) level, reduced expression of several synaptic proteins and astroglial cell markers in different brain areas 2) Increased alfa-synuclein levels; basal ganglia susceptibility to hypoxic-ischemic damage	1) Cognitive impairment 2) PD
Vasospasm, dehydration, hypercoagulable state	Brain swelling and increased intracranial pressure	+ Barometric pressure changes--> Cranial nerve palsies
Sympathetic activation	Lack of autonomic nervous system compensation (impaired chemosensitivity to hypoxia)	1) Dyspnoea in PD 2) Multiple sclerosis relapse
Vasodilation and increased CBF	Brain swelling and increased intracranial pressure	Tumors become symptomatic
Decreased oxygen delivery (hypoxemia)	Increased intracranial and cerebral perfusion pressure, increased blood-brain barrier permeability increasing free radicals' actions	Slowing brain trauma repair
PNS hypoxia	Hypoxia induces angiopathy worsening along with microtraumatic events and cold exposure	Peripheral nerve disorders
Neurotransmitters changes	Increased neuronal excitability: Sleep disturbances, dehydration, exhaustion, hypocalcemia or hyponatremia. In addition, acute severe hypoxia and respiratory alkalosis	May provoke epileptic seizure

CBF: cerebral blood flow; MS: multiple sclerosis; PD: Parkinson's disease; PFO: patent foramen ovale; PNS: peripheral nervous system; PRES: Posterior reversible encephalopathy syndrome; RCVS: Reversible cerebral vasoconstriction syndrome; TGA: Transient global amnesia.

previous history of fits without current therapy[178] or in those in treatment with antiepileptic drugs.[179] Two case were reported in male trekkers in Nepal that had a single generalized grand mal seizure without any structural (CT) or functional (EEG) abnormalities, ruled out in Kathmandu.[180] Similarly, Hennis et al[181] reported a case of a young male with a family history of seizures, who experienced an isolated tonic-clonic seizure whilst hypoxemic at 4250 m. Since in all these three cases the

mountaineers were acclimatized it is unlikely that the seizures could be related to AMS or HACE. Neuronal excitability could be increased by several physiological events such as shortage of sleep, exhaustion, dehydration, electrolyte disturbances such as hypocalcemia or hyponatremia. In addition, acute severe hypoxia and respiratory alkalosis at HA may provoke epileptic seizure. De novo seizures in people at altitude are anecdotal but may be fatal.[178] Observation on seizures at altitude are: 1. they

Table 3. Recommendations for HA exposure for neurological patients.

RECOMMENDATIONS	NEUROLOGICAL CONDITIONS
Absolute contraindications	• Unstable conditions, such as recent strokes
	• Diabetic neuropathy
	• TIA in the last months
	• Brain tumors
	• Neuromuscular disorders, with a decrease of FVC of >60%
Relative contraindications[a]	• Epilepsy based on seizure recurrence of and stabilization with the therapy
	• Parkinson's disease (±OSAS)
	• Mild Cognitive Impairment (±OSAS)
	• PFO and migraine have to be considered as a risk factor for AMS

[a]personalized decision has to be made after careful evaluation by a neurologist expert in the field.
AMS: acute mountain sickness; FVC: forced vital capacity; OSAS: obstructive sleep apnea syndrome; PFO: patent foramen ovale; TIA: transient ischemic attack.

tend to be first time fits; 2. they occur in the first 2-3 days after arrival; 3. there is an under representation of alcohol abuse; 4. fits seem to be more thalamic than cortical in origin.[41] For a single seizure occurring at altitude if any possible underlying neurological condition is ruled out there is no contraindication for future mountaineering, trekking or climbing with specific precautions as suggested by the UIAA Medical Commission and other authors.[182] For known epileptics it is advisable to continue previous antiepileptic therapy at altitude,[179] and if they discarded therapy, one should consider resuming medicines. Moreover, it is advisable avoid sleep deprivation and alcohol use/abuse, and also epileptogenic drugs.

Conclusive remarks

Mountain climbers may develop specific illnesses that largely depend on the altitude reached and the rate of ascent. The popularity of travel to HA destinations, extreme tourist activities and mountain climbing is reflected by the fact that neurologists at low altitude are increasingly likely to encounter neurological problems and disorders in people exposed to HA. Additionally, neurologists may have to advise patients with pre-existing neurological conditions on the risks of ascent to altitude. This review focuses on neurological-related HAI: AMS and HACE, as well as other neurological disorders occurring at HA and the risks posed by HA for patients with neurological disorders.

The present study examines the problems posed by HA traveling with several neurological conditions, and whether the underlying disease will worsen in the mountains (see also Table 2). The neurological conditions that allow to practice mountaineering include migraine, except with atypical aura, and other common headaches, epileptic seizures under good pharmacological control and Parkinson's disease without OSAS with precautions. All neurological patients need to attend altitude locations always accompanied. Contraindications are unstable neurological conditions (e.g., recent stroke),

diabetic neuropathy, neuromuscular disorders with a decrease FVC of >60%, Parkinson disease with OSAS, MCI and dementia, cerebral thrombosis, intracranial hemorrhage and vascular malformations, and intracranial space occupying mass.

We try to estimate the risk found by previous transient ischemia of the brain, emboli from patent foramen ovale, occlusive cerebral artery diseases, multiple sclerosis, peripheral neuropathies, neuromuscular disorders, as well as psychiatric and sleep disorders.

We provide recommendations regarding evaluation, advice for or against travelling in mountains and effective prophylactic measures since individual cases should be advised after careful examination and risk evaluation either in an outpatient mountain medicine service or by a physician with knowledge of risk involved in travelling in the mountains (Table 3).

This area has not been fully investigated and the data are in many instances either anecdotal or based on personal experience therefore further experience is needed. The main purpose of these recommendations is to avoid occurrence of acute mountain sickness or cerebral edema and recurrence of a neurological condition in a remote area where the rescue might be difficult.

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