

Travel to altitude with neurological disorders

(Recommendation of the UIAA Medical Commission)

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Abstract

The present review examines several neurological conditions and the problems posed by travelling to high altitude, and in particular whether the underlying disease is likely to worsen. The neurological conditions include migraine and other types of headaches, transient ischemia of the brain, occlusive cerebral artery diseases, intracranial haemorrhage and vascular malformations, intracranial space occupying mass, multiple sclerosis, peripheral neuropathies, neuromuscular disorders, epileptic seizures, dementia and Parkinson's disease. Attempts will be 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. Some individual cases should only be advised after careful examination and risk evaluation either in an outpatient mountain medicine service or by a physician with knowledge of travelling and high altitude risks. Recent developments in diagnostic methods and treatment of neurological conditions are also mentioned.

Keywords: altitude, mountaineering, migraine, stroke, epilepsy, seizures, Parkinson disease

Background

This paper presents the official recommendation of the Medical Commission of the UIAA (Union Internationale des Associations d'Alpinisme – International Mountaineering and Climbing Federation). The UIAA is the world umbrella organization of alpine and mountaineering federations with representatives of 68 countries worldwide. The main goal of the Medical

Commission (UIAA MedCom) is to establish worldwide standards for preventive medicine and health at altitude and in any discipline of climbing and mountaineering.

Introduction

In the evaluation of risk of high altitude exposure some neurological disorders might show a stable deficit (i.e. a previous stroke 5 years ago), a progressive (i.e. amyotrophic lateral sclerosis (ALS), vascular dementia) or improving neurological deficit (i.e. recent stroke). These latter conditions may deteriorate at high altitude and therefore some physiological considerations are useful. Persons acclimatizing well to moderate

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altitude appear to maintain brain O₂ delivery and metabolism: this is accomplished through increases in ventilation, cerebral blood flow and haemoglobin. Ventilation and oxygen delivery depend on hypoxic ventilatory response, sensitivity to CO₂ and fluid balance changes. However individual response is variable and acute mountain sickness (AMS) or cerebral oedema (HACE) might occur, although their pathogenesis is poorly understood. Metabolic studies suggest that with high altitude hypoxia there is impairment with neurotransmitters and the blood brain barrier in hypoxia does not function well. Transcranial ultrasound (2D) and MRI studies demonstrated an increase in the MCA diameter on acute exposure to both normobaric and hypobaric hypoxia [1, 2]. In acclimatized people no evidence of cerebral arteries vasodilatation was shown up to 6400 m while above this altitude vasodilatation occurs and it is reversed rapidly with supplementary oxygen [3, 4].

Another contributing factor is nocturnal hypoxemia: on the first night of arrival at altitude there is an extreme hypoxemia during sleep, this might emphasize the possible danger for many patients if they have pre-existing hypercapnia or a low ventilatory drive (i.e. bulbar cases, neuromuscular patients). Such patients appear in danger and should be protected with oxygen administration.

Migraine

There is an observed higher incidence of migraine attack at altitude. Every mountaineer with migraine knows that at altitude his headache can increase in frequency and intensity [5]. It is clear why high altitude is a trigger for migraine, since it seems to activate the trigemino-vascular system, and beyond this, there is an increased cerebral blood flow at altitude [6]. Both migraine and AMS could be possibly attributed to an activation of trigemino-vascular system that is a very important sensory input [7]. Signals generated at high altitude which may activate the trigemino-vascular system include proteins and neurotransmitters. Headache can be attributed to the activation of a common pathway in the trigemino-vascular system by both biochemical and mechanical stimulation.

Regarding migraine treatment, either aspirin or triptans might be of value, assuming the patient is not aspirin intolerant and has used this regularly beforehand. The effects of triptans act both on vasoconstriction and since they have an action on brainstem serotonergic nuclei. The use of triptans seems to be safe and recent studies also suggest some usefulness in AMS prevention [8]. In a recent Cochrane review the quality of evidence for the latter study has been degraded to a low quality due to imprecision [9]. Recommendations for people with migraine with aura and without aura are summarized in Tab. 1.

Table 1. Migraine

- It is essential that the definite diagnosis of migraine is made by a neurologist with experience in headache treatment
- Any patient who suffers from migraines must be informed that their headaches can worsen at altitude, both in frequency and/or intensity
- It's better for the migraine patients to have in their backpack a proven effective drug (aspirin, FANS or triptans) and a second drug for potential prevention treatment (e.g. flunarizine or amitriptyline)
- Recent data demonstrated the safety of triptans at altitude

Recommendations

In case of migraine with atypical or prolonged aura we recommend before travel:

- Brain MRI with diffusion weighted study to disclose recent embolic subclinical strokes.
- Blood analysis to study thrombophilic state such as protein C or S.

Transcranial Doppler to disclose patent foramen ovale (PFO) or other right to left shunts (also a possible trigger of AMS or HAPE)

Cerebrovascular disease

Ischemic stroke

Stroke is the third cause of death and the first of disability in developed countries. The global incidence of stroke varies considerably from 20/100.000 to 250/100.000. In Italy a recent study showed a slight reduction of stroke incidence [10]. About one third of stroke patients manage to maintain their independence without disability or with slight disability and resume normal activities, including travelling or recreational activities at altitude, like skiing or trekking (Tab. 2).

Scientific literature has reported case studies of possible severe strokes at altitude [11, 12], in healthy people. There is some research on the incidence of experiencing first ever stroke at altitude, but studies evaluating incidence of recurrent stroke are lacking. One study on Indian soldiers showed that the hospitalisation at high altitude for first ever stroke was more frequent (13.7/1000 versus 1.05/1000) and that stroke incidence might be higher above 3500 m [13]. Another study suggested a higher relative risk of stroke (RR 10, p < 0.05) in high altitude residents living above 4500 m compared to subjects living between sea level and 600 m [14]. Several factors that occur at high altitude can explain the possible risk increase, especially dehydration and polycythemia with consequent "inspissatio sanguinis" [15]. Hypoxia can trigger endothelial dysfunction and coagulation abnormalities and platelet aggregation [16]. Long-term stays at high altitude in association with a hypercoagulable state – in particular, congenital or acquired thrombophilia – appears to

predispose to cerebral venous thrombosis (CVT). The association of CVT with a single exposure to high altitude seems low, but the risk cannot as yet be specifically estimated [17]. Altitude may induce larger infarcts for the concomitant hypoxia and therefore expose people to higher risk of death [11]. Moreover, some research suggests the effects of hypoxia on cerebral circulation with altered cerebrovascular reactivity on the field [18] or in hypobaric chamber match-up [19].

Table 2. Recommendations for patients with ischemic stroke or TIA (Transient Ischemic Attacks)

Recent stroke (< 90 days)	There is insufficient data about safety when trekking at high altitude, therefore avoid altitude.
Patients with former stroke	<ol style="list-style-type: none"> 1. It is critical to verify the definite diagnosis of stroke (clinical history and evidence on the neuroimaging). 2. In every stroke type it is imperative the control of risk factors (arterial hypertension, hyperglycaemia, hypercholesterolemia, anticoagulation in atrial fibrillation, stop smoking). 3. In atherothrombotic stroke we recommend carotid ultrasound within previous 6 months to avoid the risk of complicated plaque or severe stenosis. 4. In cardioembolic stroke we recommend a cardiological examination and eventually echocardiography. Dosing with low molecular weight heparin is preferable to warfarin in a difficult environment. 5. Only when cryptogenic stroke is indicated should one search for other risk factors such as coagulation abnormalities or patent foramen ovale. 6. Do not trek alone. 7. A moderate or severe disability (Rankin scale > 2) is a contraindication to a wild environment. 8. TIA is often a clinical diagnosis. Remember that loss of consciousness, dizziness, falls, amnesic or confusional episodes as isolated symptoms are not necessary TIAs. No climbing or trekking alone at high altitude if previous TIA.

It is not clear what the embolic risk at altitude is. In one experimental study, hypobaric hypoxia caused aseptic vegetation on heart valves in rats after 36 hours of exposure [20]. Patent foramen ovale (PFO) or other right to left shunts are possible risk factor of embolic stroke at altitude [1]. On the other hand, recent data [21] suggest that in climbers that developed AMS there is higher prevalence of PFO carriers (63%) while in non-AMS climbers only 39% had PFO. Clinicians should consider PFO as a risk factor for AMS during climbing. These worsen during exercise [2] and were diagnosed in a hypobaric chamber when

three patients suffered TIAs at extreme altitude [19]. Hypoxia can finally induce cardiac arrhythmias [22]. It is well known that altered cerebrovascular reactivity might confer an increased risk of stroke [23] in almost any patient with pre-existing vascular risk factors such as arterial hypertension [24], diabetes mellitus [25], carotid stenosis [26], in people with white matter leukoencephalopathy and in a patient with previous recent stroke.

From the epidemiological and clinical point of view the risk of a second stroke after first ever stroke is high for at least one year [27]; after a TIA the risk of stroke and other vascular problems including vascular death is 8% at 30 days and 9.2% at 90 days [27-29]. Furthermore, a patient with previous TIA must be informed that the best treatment in case of recurrence is thrombolysis (when possible) and treatment in a stroke unit, and both these treatment options are very difficult to meet at altitude or in adverse environment.

For all these reasons, people with recent ischemic cerebrovascular diseases and patients without residual disability must be extremely carefully counseled about travelling to high altitude after careful examination and risk evaluation either in an outpatient mountain medicine service, by a neurologist, or by a physician with knowledge of travelling and high altitude risks. We know that such patients are at a higher risk to develop CVA in the 3 months subsequent to the one they suffered a TIA [28]. Therefore, the diagnosis of a CVA should be certain and we advise these patients to seek the advice of a neurologist before reaching altitude. All treatable risk factors should be first treated (such as severe carotid stenosis, blood pressure, other cardiac sources of emboli, etc.). Moreover, we also recommend checking cholesterol HDL/LDL, C-reactive protein and homocysteine levels, all markers of endothelial damage. The patient should continue treatment with antiplatelet drugs and should be advised to not exceed altitudes over 3000 m [30].

Transient Ischemic Attacks (TIA)

This is defined as a focal neurological deficit lasting less than 24 hours [29], although recent evidence has shortened this duration. The diagnosis has to be done by a neurologist (isolated vertigo or syncope are not TIAs). It is therefore advisable that a mountaineer with a possible TIA needs first a cerebrovascular work up. In the mountains a pragmatic alternative is to start treatment with aspirin, since there is no clear evidence that the mechanism of TIA and subsequent stroke risk differs at high versus low altitude. In the differential diagnosis one should consider cerebral venous thrombosis. In contrast to these rare events, syncope is common at high altitude and differential diagnosis with TIA and convulsive disorders require strict neurological criteria.

Hemorrhagic strokes

These are often due to arterial hypertension and altitude may increase blood pressure, which has an adverse effect on both cerebral aneurisms and arterial venous malformations. Patients with such conditions are advised to avoid high altitude. No study has evaluated the incidence of high altitude on the frequency of intracranial haemorrhage. Patients with lobar haemorrhage are at risk of a recurrence since it results from amyloid angiopathy. These patients should not ascend to high altitude because of difficulty in managing a recurrence of intracranial haemorrhage in a remote area.

Tumors and other lesions

Patients with intracranial lesions are neurologically unstable and should not travel to altitude [31]. Several explanations and case reports support this advice. According to the Monroe-Kellie doctrine, any increase in any one of the volumes of the brain, blood or cerebrospinal fluid volume (CSF) is compensated with the reduction of the other two; however, once these compensative measures are exhausted, an elevation of intracranial pressure (ICP) occurs. According to this mechanism, in patients with intracranial lesions when exposed to hypoxic environment, failure of these compensating measures can cause ICP raise and brain swelling, and if not treated global ischemia and brain death might happen. Indeed, cerebral oedema that occurs at high altitude is reflected by an increased tissue water content and swelling of perivascular glial endfeet. There are reports of brain tumors both malignant and benign which suddenly become symptomatic when people are exposed to high altitude [32, 33] or during long commercial flight [34-36]. This might be due to oedema, an increase in cerebral blood flow, or increased cerebrospinal fluid pressure. A similar problem is presented by arachnoidal cysts [37].

Brain trauma, head concussion and metabolic dysfunction

The time required for the brain repair itself following a common brain trauma is not well understood, especially at high altitude where the brain repair resulting from a concussion is likely to be slow. Indirect evidence suggests that an increased blood-brain permeability enhancing action of free radicals is possible.

It is also known that hypoxia is one of the possible secondary insults that affects short and long-terms outcomes and is associated with poorer neurological outcome of traumatic brain injury (TBI) patients [38]. In addition, elevated hemoglobin concentration due to chronic hypoxic exposure, commonly present

in long-lived inhabitants of the Tibetan plateau region, has been shown to have a deleterious effect on recovery and mortality of patients with acute severe head trauma after decompressive craniectomy [39]. In conclusion, for a patient with a traumatic or a metabolic brain injury (such as CO poisoning) or previous brain hypoxia or metabolic dysfunction after a cardiovascular operation it does not seem advisable to go at high altitude.

Multiple sclerosis (MS)

Patients with MS might be considered safe up to 2500 meters. MS patients may develop new neurological signs and symptoms if they present an infection or if exposed to cold; moreover, an exacerbation of a relapsing remitting MS was recently reported with exposure to high altitude (Mt. Fuji at 12,388 feet / 3,776 meters) [40]. Therefore, prolonged exposure to such unfavorable conditions does not seem advisable.

MS is an autoimmune disease and repetitive proinflammatory cascades could also act at the endothelial level causing decreased vasodilatory capacity, which limits blood supply for neurons performing demanding tasks and therefore leading to overproduction of nitric oxide (NO), which, in turn, contributes to the secondary neurons degenerative damage [41]. This cerebral vasoreactivity (CVR) impairment has been recently found to be related in MS to cognitive decline. The physiopathological description of hypoxia related damage in acute inflammatory lesions [42] coupled with the reduced CVR strongly suggests that patients with MS must be advised to avoid altitude to prevent a possible new relapse, even when symptoms are mild. Moreover, 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.

Dicianno et al. found, at the National veterans Winter Sports Clinic (NVWSC) in Colorado (elevation between 2470 and 3813), in the athletes with several neurological disabilities (spinal cord injury, traumatic brain injury, multiple sclerosis, stroke and other neurological impairments), an overall higher occurrence of AMS and particularly in 3 of the 5 athletes with multiple sclerosis (60%) [43]. Subsequently, they reported in 2013 data collected over three years (2007, 2008 and 2009) with a higher number of participants and they found that athletes with neurological impairment showed a higher mean LLS score compared to healthy controls and that the presence of a neurological impairment, prior history of AMS and prior history of headache at HA were correlated with higher LLS [44].

In conclusion, a careful personalized investigation should be performed in each patient, before the clinicians can advise properly patients with MS to whether or not they could go to HA.

Peripheral nerve disorders and neuromuscular diseases

In sensory motor peripheral neuropathies both of inherited or acquired cause clearly there is risk related to the relative insensitivity of the foot during walking or climbing. In diabetic neuropathy there is in addition a microvascular abnormality [45]. It is important that such patients wear comfortable shoes that are not tight to help promote a continuous blood flow to peripheral extremities, since the activity of skeletal muscles and their body temperature is critical. When purchasing climbing shoes find a climbing shoe that fits the shape of your feet, including existing deformities. Foot size may also be slightly larger in hot weather, after standing for some hours, during menstrual cycle or at altitude where there is slight oedema in the feet of women.

The present recommendations are that such patients should stay hydrated, avoid immobility to prevent deep venous thrombosis and walk with warm comfortable stockings for mountaineering, flight socks when flying. There is no evidence that previous peripheral damage can progress at altitude. We followed a 33-year-old patient who, one year after a Guillain-Barré syndrome, went up to 8100 m on Mount Everest without recurrence (personal data, not published). Paulson et al. 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 [46].

Many patients with muscular dystrophies, such as Duchenne's muscular dystrophy or myotonic dystrophy and amyotrophic lateral sclerosis, can have alveolar hypoventilation with hypoxemia and sleep disturbances, including sleep apnoea, with consequent nocturnal hypoxemia that arrive at oxygen saturations as low as 75% at sea level. It is easy to imagine that these patients can have more desaturations at altitude. Therefore, patients with neuromuscular disorders should be screened for the presence of sleep apnoea prior to travel at high altitude and, if sleep disturbance is detected, they should travel with non-invasive ventilatory support [47].

Seizures at altitude

There are case reports of new onsets of seizures at high altitude outside the usual setting of AMS or HACE [48], as well as occurrence of seizures in persons with remote history of fits without therapy [49] or in treatment with antiepileptic drugs [50]. Two male trekkers in Nepal presented single generalized grand mal seizures with tonic-clonic jerks, tongue bite and post-ictal confusion [51]. Extensive medical investigations in Kathmandu including CT and EEG did not reveal any abnormality and

both were seizure free in the following years. The pathophysiology of these single seizures was unlikely related to AMS or HACE since both mountaineers had adequate acclimatization. Seizures may result from any physiological event determining an increase neuronal excitability including shortage of sleep, exhaustion, dehydration, electrolyte disturbances such as hypocalcemia or hyponatremia [51]. Acute severe hypoxia may cause epileptic seizure (Tab. 3). De novo seizures in people at altitude are anecdotal but may be fatal [49]. Observation on seizures at altitude are:

- They tend to be first time fits.
- They occur in the first 2-3 days after arrival.
- There is an under representation of alcohol abuse.
- Fits seem to be more thalamic than cortical in origin.

For known epileptics it is advisable to stay on previous antiepileptic medicine at altitude [50], avoid lack of sleep and alcohol use, avoid also epileptogenic drugs; if they discarded therapy one should consider resuming medicines. In persons with seizure disorders exacerbations possibly due to altitude or lack of sleep have been observed, at least in those not on medication.

Table 3. Epilepsy

-
- In hypoxia some GM crises have been reported
 - Epileptic patients need continuous drug level check
 - Epileptic patients should avoid alcohol intake
 - Sleep deprivation might be dangerous
-

Dementia

Higher cortical function which includes cognitive and psychiatric aspects has been reported to be affected by acute or chronic altitude exposure in normal subjects [52]. It is also known that hypoxemia is a crucial factor for cognitive impairment in patients with pulmonary (e.g. COPD) [53, 54] and cardiopulmonary disorders [55, 56] and that the degree of cognitive impairments is closely related to the degree of hypoxia.

In animal studies it has been shown that hypoxia increased β -amyloid ($A\beta$) generation in aged AD mice and increased phosphorylation of tau in prenatal hypoxic mice, decreased hypoxia-induced factor, and enhanced activation of astrocytes and microglia [57]. Data about dementia and altitude are scarce. Well-adapted elderly Andean high altitude dwellers compared to lowlanders showed a slightly impaired cognitive function [58-60]. However, in a study performed in a less developed areas of sub-Saharan Africa and South Asia on 481 residents at altitude (between 2100 m and 4000 m asl) aged > 60 years who underwent a cognitive screen, 1.37% were classified as

cases of Mild Cognitive Impairment (MCI) whereas the 98.8% of the subjects scored within normal range. The contradictory results may depend in the latter case on specific population characteristics (e.g. illiterate) but also could be related with the reduced environmental and cardiovascular risk factors in such population [61]. Due to the potential deleterious effect exerts by hypoxia on cognitive functions it is not advisable to allow patients with dementia to go to altitude and this could be applied also to MCI patients. MCI is a condition in which individuals demonstrate cognitive impairment with minimal impairment of instrumental activities of daily living and is considered to be an intermediate state between normal cognitive aging and early dementia [62]. However, many individuals are found to be cognitively normal in follow-up assessments and a meta-analysis that assessed reversion rates in 25 studies indicated an overall reversion rate of approximately 24% [63]. Several factors (e.g., life style) have been implicated in MCI reversion. However, it is not yet established whether hypoxia exposure may contribute to the progression of the MCI into dementia. Finally, 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 [64]. In a murine model of AD has been shown that IH improves cognition [65].

Parkinson's disease (PD)

PD is related to the neurodegeneration of the nigrostriatal dopamine system that lead to a decreased dopaminergic transmission in the basal ganglia. Basal ganglia are particularly susceptible to hypoxia-ischaemia due to their high metabolic activity [66]. Hypoxia inducible factor (HIF1A) is known to play an important role in the pathogenesis of neurodegenerative disorders and has been suggested to contribute to PD pathogenesis [67]. An impaired chemosensitivity to hypoxia and perception of dyspnoea was also reported in PD's patients [68]. Recently has also been reported that chronic intermittent hypoxia due to obstructive sleep apnea syndrome (OSAS) contributes to the pathogenesis of PD increasing the α -synuclein levels [69]. Moreover, 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.

One case of Parkinsonism after acute hypobaric hypoxia exposure (up to 16,000 ft – 4,877 m) resulting in damage of the basal ganglia has been reported [70]. However, there are no published data in the literature regarding patients with idiopathic PD

travelling to altitude. Few studies were performed to evaluate the effects of a 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 [71, 72].

With the abovementioned premises, screening for the presence of sleep apnoea is advisable prior to travel at high altitude and, if sleep disturbance is detected, they should travel with non-invasive ventilatory support [47]. Risk factors known to be related with altitude exposure should be assessed in PD patients (e.g., prior history of AMS, prior history of headache at HA, etc.) and specific recommendations are that every parkinsonian patient needs always to visit the mountain accompanied, needs to maintain adequate hydration and to have their own specific oral antiparkinsonian drugs promptly available. Furthermore, patients with PD and other comorbidities need to be carefully evaluated by a neurologist expert in the field.

COVID-19 (or SARS-CoV-2) infection and neurological complications

Recent evidence has shown that COVID-19 can determine several neurological dysfunctions such as hyposmia [73], Guillain-Barré syndrome [74], CNS lesions, impaired consciousness and thrombosis [75, 76]. Therefore, people that have had COVID-19 infection should be examined by a neurologist. On the other hand, it has been reported a possible lower incidence of COVID-19 at high altitude according to epidemiological data [77, 78]. However, these data should be considered preliminary and speculative as it has been discussed in a recent paper by Pun et al. [79].

Pulmonary infection in COVID-19 although similar has different pathogenic mechanisms from HAPE [80]. It is unknown if previous COVID-19 infection predisposes to AMS, HACE or HAPE.

Conclusion and contraindications

In addition to the above guidelines, we give the following certain relative or absolute contraindications to high altitude exposure:

1. Unstable conditions – such as recent strokes
diabetic neuropathy.
2. TIA in the last month.
3. Epilepsy.
4. Brain tumors.
5. Neuromuscular disorders with a decrease of FVC of > 60% (Tab. 4).

6. Parkinson's disease (\pm OSAS).
7. Mild Cognitive Impairment (\pm OSAS).
8. PFO has to be considered as a risk factor for AMS during climbing.
9. Migraine with atypical aura (\pm PFO) can be a relative contraindication.

Therefore, each case must be carefully assessed individually before going to altitude. There should be no risk to exposition at high altitude for patients with:

1. Demyelinating disease up to 2500 m.
2. Peripheral nerve problems up to 2500 m.
3. Minimal neurological dysfunction.

Table 4. Demyelinating diseases and PNS / muscle disorders

Multiple sclerosis	<ul style="list-style-type: none"> • Cold climate should be avoided • No mountain trekking if disability by RANKIN scale > 2 • No trekking if vertigo or ataxia
Peripheral neuropathies	<ul style="list-style-type: none"> • No trekking for Charcot-Marie Tooth disease: stumbling might be dangerous for presence of clubfoot • Diabetic neuropathy: small vessel ischemia in diabetes; hypoxia might be a contraindication
Neuromuscular disorders and motor neuron disorders	<ul style="list-style-type: none"> • Decrease of FVC > 60% is a contradiction to high altitude travel for hypercapnia and hypoxia • Decrease in bulbar central drive: risk of sleep apnea is increased in myotonic dystrophy, ALS and adult type glycogenosis type 2

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G. Giardini from the Neurological Division and Mountain Medicine Service, Aosta Hospital (Italy) and M. Falla from the Center for Mind / Brain Science, University of Trento, Rovereto (TN), Italy, were working as guest authors for the commission.

History of this recommendation paper

The paper is based mainly on a lecture held by C. Angelini at the UIAA MedCom Annual Meeting at Aviemore, Scotland, October 2007 and updated in 2009. The version presented here was approved by written consent in lieu of a live meeting in January 2021.