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Travel to Altitude with Neurological Disorders

Intended for Doctors, Interested Non-medical Persons and Trekking or Expedition Operators

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1. 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 and epileptic seizures. 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.

2. 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. amyotropic 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 altitude appear to maintain brain O_2 delivery and metabolism: this is accomplished through increases in ventilation, cerebral blood flow and haemoglobin. Ventilation and oxygen delivery depends on hypoxic ventilatory response, sensitivity to CO_2 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. There might be an increase of cerebral blood flow at high altitude, even if this is difficult to demonstrate since cerebral Doppler measurements are unreliable.

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 subministration.

3. Migraine

There is an observed higher incidence of migraine attack at altitude. Every mountaineer with migraine knows that at altitude his headache can increases in frequency and intensity (Serrano-Duenas, 2007). 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 at altitude an increased blood flow. Both migraine and AMS could be possibly attributed to an activation of trigemino-vascular system that is a very important sen-

sory input (Sanchez del Rio and Moskowitz, 1999). Signals generated at high altitude which may activate the trigemino-vascular system include proteins and neurotransmitters. A headache can be attributed to the activation of a common pathway in the trigemino-vascular system by both biochemical or mechanical stimulation.

Regarding migraine treatment, either aspirin and 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 serotoninergic nuclei. The use of triptans seems to be safe and recent studies also suggest some usefulness in AMS prevention (Jafarian et al., 2008). Recommendations for people with migraine with aura and without aura are summarized in table 1.

Table 1: Migraine

• It is essential that the definite diagnosis of migraine be 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 patient to have in their backpack a proven effective drug (aspirin, FANS or triptans) and a second drug for eventual prevention treatment (e.g. flunarizine or amitriptiline) • Recent data demonstrated the safety of triptans at altitude
Recommendations In case of migraine with aura we recommend before travel: – Brain MRI with diffusion weighted study to disclose recent embolic subclinical strokes – Blood analysis to study thrombophilic state Echocardiography to disclose patent foramen ovale (PFO) or other right to left shunts (also a possible trigger of AMS or HAPE)

4. Cerebrovacular disease

4.1 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 (Corso, 2009). 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 ski or trekking (Table 2).

Scientific literature has reported case studies of possible severe strokes at altitude (Clarke, 1983; Sharma, 1990) 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 3500m (Jha et al., 2002). Another study suggested a higher relative risk of stroke (RR 10, $p<0.05$) in high altitude residents living above 4500m compared to subjects living at 600m at sea level (Niaz, 2003). Several factors that occur at high altitude can explain the possible risk increase, especially dehydration and polycythemia with consequent "inspissatio sanguinis" (Clarke, 2006). Hypoxia can trigger endothelial dysfunction and coagulation abnormalities and platelet aggregation (Le Roux et al., 1992). Altitude may induce larger infarcts for the concomitant hypoxia and therefore expose people to higher risk of death (Clarke, 1983). Moreover some research suggests the effects of hypoxia on cerebral circulation with altered cerebrovascular reactivity on the field (Van Osta et al., 2005) or in hypobaric chamber (Cauchy, 2001).

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

Recent stroke (<90 days)	There is insufficient data data about safety when trekking at high altitude, therefore avoid altitude
Patients with former stroke	1. Is critical to verify the definite diagnosis of stroke (clinical history and evidence to the neuroimaging). 2. In every stroke type it's 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 criptogenic 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's 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 hour of exposure (Nakanishi et al, 1997). Patent foramen ovale (PFO) or other right to left shunts are possible risk factor of embolic stroke at altitude (Wilson, 2009). These worsen during exercise (Imray, 2008) and were diagnosed in a hypobaric chamber when 3 patients suffered TIAs at extreme altitude (Cauchy, 2001). Hypoxia can finally induce cardiac arrhythmias (Woods, 2008). It is well known that altered cerebrovascular reactivity might confer an increased risk of stroke (Terborg et al., 2000) in almost any patient with pre-existing vascular risk factors such as arterial hypertension (Ficzere et al., 2001), diabetes mellitus (Fulesdi et al., 1997), carotid stenosis (Silvestrini et al., 2000), in people with white matter leukoencephalopathy (Molina et al., 1999) 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 (Giles and Rothwell, 2009); 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 (Hill et al., 2004; Johnston et al., 2000; Giles and Rothwell, 2009). 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 counselled about travelling to high altitude after careful examination and risk evaluation either in an outpatient mountain medicine service, 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 (Hill et al., 2004). 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 homocisteine levels, all markers of endothelial damage. The patient should continue treatment with antiplatelet drugs and should be advised to not exceed altitudes over 3000m (Richalet and Herry; 2006).

4.2 Transient Ischemic Attacks (TIA)

This is defined as a focal neurological deficit lasting less that 24 hours (Johnston et al., 2000), 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 an cerebrocascular work up. In the mountain 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.

4.3 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.

5. Tumors and other lesions

Patients with intracranial lesions are neurologically unstable and should not travel to altitude (Baumgartner et al., 2007). 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 tumours both malignant and benign which suddenly become symptomatic when people are exposed to high altitude (Hackett, 2001). 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.

6. 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 an increased blood-brain permeability enhancing action of free radicals is possible.

For a patient with 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.

7. Multiple sclerosis

Patients with MS may be considered safe up to 2500 meters. Baumgartner et al. (2007) observed that MS patients during summer campus in Colorado mountains were safe. MS cases may develop new neurological signs and symptoms if they present an infection. Cold may also be an aggravating factor in demyelinating disorder, therefore prolonged exposure to such unfavourable conditions does not seem advisable. Although recent works showed no evidence of cerebral vasoreactivity impairment in patients with MS (Uzuner et al., 2007), the physiopatholological description of hypoxia related damage in acute inflammatory lesions (Bruck and Stadelman, 2005)

strongly suggests patients must be advised to avoid altitude to prevent a possible new relapse, even when symptoms are mild.

8. 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. 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 8100m on Mount Everest without recurrence (personal data, not published). Paulson et al. (2002) found that Charcot Marie Tooth patients were at risk of developing dysartria, incoordination and difficulty walking after returning from skiing at 8000 ft in the Colorado mountains (Paulson et al; 2002).

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's 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 (Luks and Swenson, 2007).

9. Seizures at altitude

There are case reports of new onsets of seizures at high altitude outside the normal setting of AMS or HACE (Daleau et al., 2006), as well as occurrence of seizures in persons with remote history of fits without therapy (Basnyat, 1998) or in treatment with antiepileptic drugs (Basnyat, 2001). Two male trekkers in Nepal presented single generalized grand mal seizures with tonic-clonic jerks, tongue bite and post-ictal confusion (Kupper and Classen 2002). 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 distur-

bances such as hypocalcemia or hyponatremia. Acute severe hypoxia may cause epileptic seizure (Table 3). De novo seizures in people at altitude are anecdotal but may be fatal (Basnyat, 1998). 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 (Basnyat 2001), 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 should avoid alcohol intake
• Sleep deprivation might be dangerous

10. Conclusion and contraindications

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

1. unstable conditions - such as recent strokes
2. diabetic neuropathy
3. TIA in the last month
4. epilepsy
5. brain tumors
6. neuromuscular disorders with a decrease of FVC of >60% (Table 4)

Migraine, almost with aura, 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 2500m
2. peripheral nerve problems
3. minimal neurological dysfunction

Table 4: Demyelinating diseases and PNS / muscle disorders

Multiple sclerosis	▪ Cold climate should be avoided ▪ No mountain trekking if disability by RANKIN scale >2 ▪ No trekking if vertigo or ataxia
Peripheral neuropathies	▪ 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	▪ 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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