High altitude exposure and ischemic stroke: A literature review

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High altitude exposure and ischemic stroke: A literature review

Esteban Ortiz-Prado (1,2) Jeff F. Dunn (3)

Abstract

Despite our understanding of stroke, the risk factors involved and its treatment and prevention, stroke remains the second leading cause of death among humans worldwide. Several risk factors have been associated with higher incidences of stroke, such as hypertension or diabetes, while non-traditional risk factors such as vitamin D deficiency or cardiac valvular thickness have recently been identified. The potential role of hypoxia or high altitude exposure as a risk factor has not been clearly established. This review includes the relationship between acute and chronic high altitude exposure and the possible development of ischemic stroke in high altitude populations. Several risk factors are identified in high altitude dwellers such as polycythemia, increased platelet adhesiveness and greater risk to develop vascular thrombosis. Other conditions such as dehydration, extreme cold and immobilization might lead to increased risk of ischemic stroke in newcomers. Taking into account the limited number of studies, it is argued that high altitude and chronic hypoxia may be risk factors for the development of ischemic stroke. The altitude associated with higher prevalence of ischemic stroke is not clear, but it appears that there is increased risk above 3000m.

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Introduction

Although extensive research has been carried out to understand the pathophysiology, etiology, risk factors and management of stroke, the role of hypoxic exposure as a risk factor is uncertain. Probing the role of hypoxia will be valuable in understanding the mechanism of stroke induction and beneficial for developing countries which are located at high altitude [1-3]. Hypoxia in this case is defined as a reduction in the relative levels of oxygen (either inspired or at the level of substrate delivery). Tissues have a chronic and acute response to hypoxia that involve genetic responses on the one hand, and acute metabolic and physiological changes on the other. As a result, this review makes a distinction between those living at altitude vs. those visiting from lower regions.

Although the literature in this area is sparse, there are key epidemiological reports available. In this review we discuss the epidemiological factors with stroke prevalence among various groups at high altitude and the impact of hypoxia on select risk factors.

Epidemiological overview

Establishment of epidemiological impact of high altitude hypoxia on the development of stroke is very hard because of the presence of multiple variables which are difficult to con-
It has been anecdotally noted that ischemic stroke is more prevalent in high altitude populations, and several cases of ischemic or thrombotic events have been reported in the literature as early as 1920; Table 1.

More recent references have more controlled observations. In El Cusco-Peru (3380m) stroke was reported to have a crude prevalence rate of 6.47 per 1000, certainly higher compared to values reported in previous studies (3.6/1000 in Quiroga-Ecuador, 1.3/1000 in Kashmir-Pakistan and 1.74/1000 Santa Cruz-Bolivia), Figure 1.

In India the prevalence of stroke in soldiers living at 4200m was 13x higher (13.7/1000), compared with populations living at lower altitudes (1.05/1000). The length of exposure and polycythemia were described as the more important risk factors. It is important to note that this group of soldiers were healthy and relatively young (90% <45 years) which reduced the likelihood of other age related risk factors (just one soldier was reported to be a smoker).

In addition, the severity of ischemic stroke seems to be greater in the high altitude group. The presence of massive infarction areas (>50% of the affected hemisphere) were seen in almost 50% of the patients from the high altitude group which is significantly higher than the 14% reported from the low altitude control group.

In Pakistan, a relatively large study with 4000 subjects between the ages of 20-40 years, residing at >4571m studied the prevalence of stroke in high altitude populations. All cases of stroke were included. During the same period 4000 subjects living in Rawalpindi (610m) were also observed as a race matched control group. They reported 10 positive cases of stroke at high altitude and just one case in the low altitude group. They concluded that living at high altitudes is associated with 10 times more risk of having a stroke, especially in young people between the ages of 20 and 40 years. Granted the numbers of strokes are small, this study shows a marked difference in incidence between lowland and highland populations.

In 2001, Anand et al. reported the most prevalent thrombotic complications caused

### Table 1. Anecdotic stroke cases related with altitude reported in the literature

<table>
<thead>
<tr>
<th>Date</th>
<th>Altitude (m)*</th>
<th>Clinical presentation</th>
<th>Author (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1895</td>
<td>4300</td>
<td>Right hemiparesis</td>
<td>Roverovsky (1896)</td>
</tr>
<tr>
<td>1924</td>
<td>6000</td>
<td>Hemiparesis</td>
<td>Norton (1925)</td>
</tr>
<tr>
<td>1943</td>
<td>6400</td>
<td>Dysphasia</td>
<td>Shipton (1943)</td>
</tr>
<tr>
<td>1982</td>
<td>8200</td>
<td>Left hemiparesis</td>
<td>Clarke (1983)</td>
</tr>
<tr>
<td>1986</td>
<td>7000 to 8000</td>
<td>Transient ischemic attack</td>
<td>Wohns (1986)</td>
</tr>
<tr>
<td>1990</td>
<td>4800</td>
<td>Right hemiparesis</td>
<td>Sharma (1990)</td>
</tr>
<tr>
<td>1997</td>
<td>7600</td>
<td>Right hemiparesis, radiological signs of edema</td>
<td>Basnyat (1997)</td>
</tr>
<tr>
<td>2002</td>
<td>5472</td>
<td>Anterior ischemic optic neuropathy</td>
<td>Bandyopadhyay (2002)</td>
</tr>
</tbody>
</table>

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**Table 1. Anecdotic stroke cases related with altitude reported in the literature**

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**Figure 1.** In this graph we show the relationship between high altitude and the prevalence of stroke in several cities around the globe.
by long term stay at high altitudes (3000 to 5000m). They found that the risk of ischemic stroke is 30x higher compared with lower altitude populations.

Al Tahan, Buchur et al. using a case-control study described the risk factors associated with stroke in Saudi Arabia among patients living at 620m vs. those living at >2000m. They reported that the frequency of thrombotic stroke at high altitude to be higher compared with the low altitude group (93.4% vs. 79.3%). Cruz et al. [21] reported a crude stroke prevalence ratio of 3.6/1000 in the Andean village of Quiroga-Ecuador (2300m), which was higher compared with race-matched populations located at a lower altitude [18].

The elevation at which stroke starts to be more prevalent is hard to determine, however Mahajan et al. analyzed data from 100 patients admitted at a tertiary hospital in Himachal Pradesh-India located at moderate altitude (2200m), and compared them with matched controls settled below 1000m. The prevalence of stroke in people residing at moderate altitude was reported to be lower than those residing below 2000m. Although ischemic stroke was found to be more prevalent than hemorrhagic stroke, polycythemia was not found to be a significant risk factor in this population. This suggests that the altitude was not enough to cause acclimatization, thus, the onset of polycythemia and high hematocrit levels, two important risk factors associated with ischemic stroke [2, 3, 20].

Although the above are not large studies, there is strong evidence that high altitude living both in sojourners and native populations is associated with an increased risk of ischemic stroke. We hypothesize that this risk is associated, in part, with high altitude acclimatization. The following discussion identifies risk factors associated with altitude that may contribute to this increased risk.

**Risk factors at high altitude**

In this section we described the prevalence of multiples stroke risk factors among newcomers or high altitude residents. Even thought the division between these two groups is difficult since just very few studies are available, we commented when needed and described in the following section and key points are summarized in table 2.

**Polycythemia**

Despite the advantages of increased blood carrying capacity at high altitudes, polycythemia also increases the risk of thrombus formation [11]. Polycythemia is probably the most important risk factor associated with ischemic stroke during high altitude exposure, either in newcomers or high altitude residents [2, 3, 22-25].

High hematocrit levels and polycythemia produces high blood viscosity and inadequate blood flow, which are both associated with thrombus formation [24]. These conditions, aggravated by the fact that hypoxia induces vascular endothelial damage and possible platelet aggregation, enhance the thrombotic processes [27], and in so doing are likely to increase the risk of developing stroke during high altitude exposure.

**Thrombosis and embolism**

During pathological conditions, thrombo genesis can cause severe and deleterious clinical manifestations. Some conditions, such as decreased physical activity [28, 29], increased hematocrit [30-33], or cold temperature [34, 35] have been associated with pathological thrombus formation.

The extremely low ambient temperature and the consequent peripheral vasoconstriction causes restriction of blood flow to the extremities. In addition, the physical inactivity and forced immobility, aggravated by progressive dehydration, might facilitate clot formation and causes arterial or venous thrombosis, especially in relatively newcomers (<10 months) populations [27].

High altitude exposure, has been linked per se with increased risk to develop arterial or venous thrombosis [28, 30, 31], which might lead into death [28]. This exposure has been associated with deleterious results especially in low altitude residents who visited high altitudes locations.

Long term stays in high altitude locations (>10 months) have been associated with 30 times higher risk of spontaneous vascular thrombosis in unacclimatized subjects [28, 39].

It may be that thrombosis is a relatively common complication after high and extreme altitude exposure. The exactly mechanism involved is not clear yet, however, the effects of hypoxia in platelet adhesiveness and polycythemia, facilitated by presence of different
Table 2. Clinical or environmental conditions affecting the prevalence of stroke during high altitude exposure.

<table>
<thead>
<tr>
<th>RISK FACTORS</th>
<th>DURING HYPOXIA</th>
<th>RELEVANT COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polycythemia and high Hematocrit</td>
<td>Increased</td>
<td>The most important stroke risk factor found in high altitude populations, causing blood stasis, endothelial damage and reduce blood flow</td>
</tr>
<tr>
<td>Platelet adhesiveness</td>
<td>Increased</td>
<td>Higher adhesiveness, strong evidence supporting the fact that after acute exposure, platelets become “stickier”</td>
</tr>
<tr>
<td>Thrombosis and embolism</td>
<td>Increased</td>
<td>Higher prevalence of thrombotic related events at high altitude compared with matched control groups</td>
</tr>
<tr>
<td>Obesity</td>
<td>Increased?</td>
<td>Obesity is increased at high altitude populations??</td>
</tr>
<tr>
<td>Coagulation at high altitude</td>
<td>Unclear</td>
<td>Auto-induced cascade activation, especially in AMS, HAPE, HACE increased pro and anti coagulant factors</td>
</tr>
<tr>
<td>A-V shunting</td>
<td>Increased</td>
<td>It is theorized that increased systemic flow would increase the possible transfer or emboli through pulmonary shunts and a patent foramen ovale</td>
</tr>
<tr>
<td>Platelet count</td>
<td>Increased, normal or decreased</td>
<td>Unclear below 4500m increased above this elevation.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Reduced</td>
<td>Lower prevalence in high altitude populations, reflected with lower prevalence of hemorrhagic stroke</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Reduced</td>
<td>It is hypothesized that more active life style is found amongst highlanders, since highlanders living at sea level gain weight</td>
</tr>
<tr>
<td>Diabetes mellitus type II</td>
<td>Reduced</td>
<td>Apparently lower prevalence of DMII at high altitude, despite the fact that obesity seems to be more prevalent</td>
</tr>
<tr>
<td>Atherosclerosis and lipid profiles</td>
<td>Reduced</td>
<td>Higher levels of HDL, lower prevalence of atherosclerosis, better lipid profiles, lower complications caused by atherosclerosis.</td>
</tr>
</tbody>
</table>
conditions such as cold or immobilization, are maybe responsible for such an increase in the risk of thrombosis and ischemic stroke during high altitude exposure, especially in non-acclimatized subjects.

**Platelet count and platelet adhesiveness**

Simulated high altitude exposure (>3000m) has been associated with increased platelet adhesiveness, which may increase clotting and thrombosis formation [4, 38, 42]. The mechanism of this apparently higher adhesiveness is not totally understood [43, 64], however, stronger adhesiveness causes reduced blood flow in compromised vessels [41]. This, in turn, causes endothelial tone control failure which results in arterial vasospasm within the cerebral circulation [43].

The number of platelets circulating throughout the vessel and its adhesiveness are important variables. A higher platelet count with higher adhesiveness will facilitate clot and thrombus formation, which might lead to higher incidences of pathological states, such as thrombosis.

Hypobaric hypoxia has been associated with either a reduction the number of circulating platelets [39, 44], increase [39, 47, 48], or no change [44]. However, a recent prospective cohort study found that platelet count is increased by 70% after 8 months of chronic hypoxia exposure above 3500m suggesting that chronic exposure will lead into acclimatization and therefore stronger adhesiveness [39].

**Coagulation at high altitude**

Hypercoagulability has been noted during high altitude acclimatization, and has been found to operate as an important risk factor for ischemic stroke [4, 47, 55].

However, Crosby et al, in 2003 reported the activation of the coagulation cascade, might not occur in a range of 3600m for unacclimatized subjects and 4600m in fully acclimatized human beings [41].

More recent studies have found a phased change in the coagulation cascade, rather than alterations in cofactors or proteins concentrations. Significant initial prothrombotic states, followed by a compensatory increased capillary fragility and increased bleeding time have been reported [45]. Increased levels of serum fibrinogen, higher levels of serum thromboplastin, β-thromboglobulin and platelet factor 3 were also reported during acute and chronic hypoxia [39, 44].

On the other hand, evidence of widespread intravascular clotting which is associated with and may result from reduced fibrinolytic activity with increased plasma fibrinogen, increased factors V, VIII and X, decreased factor XII, and increased platelet adhesiveness and platelet factor 3 and electrophoretic mobility of platelets reduced were reported [44, 53–55]. However, these results are in conflict with “Operation Everest II”, where no changes in coagulation were shown at 8000m [46, 57].

We conclude that some pro-coagulation factors have been shown to be increased at high altitude, especially above certain elevation, however, the literature is still conflicting.

**Arteriovenous shunting**

Hypoxia may increase the risk of peripherally induced clots passing directly from the venous to the arterial system, thereby gaining access to the cerebral circulation. Acute hypoxia is known to increase shunt flow by over 50% in the lung [58]. The maximum diameter of these shunts remains to be determined but they are certainly over 50um, even during normoxia [49]. The existence of a patent foramen ovale is also being increasingly recognized as a risk factor for ischemic stroke [45].

It is worth considering that, since flow through such shunts would increase with increased cardiac output, the possibility of transfer of a venous embolus to the arterial system by this route would increase with altitude.

**Atherosclerosis and lipids**

The prevalence of atherosclerosis is hard to determine in high altitude populations, and its relationship with the development of ischemic stroke has never been reported. However, the presence of cardiovascular diseases at high altitude caused by atherosclerosis seems to be lower [61–63].

The relationship between this low prevalence of cardiovascular diseases, caused specifically by atherosclerosis, might be related to the fact that increased high density lipoproteins (HDL) are found in high altitude residents [1, 64, 65]. Higher levels of HDL are associated with a reduced risk of developing stroke [64–68]. A recent study found that serum leptin levels, a newly discovered risk factor for ischemic stroke [65].

Lipid profiles seems to be better in high altitude populations, suggesting that other factors, such as hypoxia are more often the cause of the development of cerebrovascular diseases during high altitude exposure.
Conclusions

It is argued in this review that altitude exposure is associated with an increased risk of ischemic stroke in both residents and sojourners. This conclusion is supported by a range of epidemiological and observational studies, associating several risk factors with increased risk to developing ischemic stroke at altitude. These include 1) polycythemia, 2) stronger platelet adhesiveness, 3) increased levels of thromboplastin, 4) blood stasis aggravated by the presence of polycythemia, endothelial damage and hyperviscosity 5) prolonged immobility, 6) and increased chances of dehydration which are potential risk factors for the development of stroke. The altitude associated with higher prevalence of ischemic stroke is not clear, but it appears that there is increased risk above 3000m.

References


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Conflict of interest

None declared by authors.


Exposición a las grandes alturas y accidente cerebrovascular isquémico: Revisión de la literatura

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Resumen

A pesar de nuestra comprensión de los factores de riesgo, tratamiento y prevención del accidente cerebrovascular, éste sigue siendo la segunda causa de muerte entre los seres humanos en todo el mundo. Varios factores de riesgo se han asociado con una mayor incidencia del accidente cerebrovascular, incluyendo la hipertensión arterial y la diabetes mellitus tipo 2, mientras que los factores de riesgo no tradicionales, tales como: la deficiencia de vitamina D o el engrosamiento valvular cardiaco recientemente han sido identificados. El papel potencial de la hipoxia o la exposición a grandes alturas como factores de riesgo no se han establecido claramente. Esta revisión analiza la relación entre la exposición aguda y crónica a altitudes más altas y el riesgo de accidente cerebrovascular isquémico. En las poblaciones residentes en grandes alturas varios factores de riesgo están presentes, tales como: policitemia, aumento en la adhesividad plaquetaria y una mayor prevalencia de trombosis vascular. Otras condiciones como: la inmovilización, pueden conducir a un incremento en el riesgo en el accidente cerebrovascular isquémico en las regiones con altitudes altas. La altitud asociada con una mayor prevalencia del accidente cerebrovascular isquémico no está bien definida, pero parece que existe un mayor riesgo por encima de los 3000 metros.

Palabras clave
Grandes alturas, Hipoxia, Accidente cerebrovascular isquémico, Poliglobulia, Adhesividad plaquetaria, Trombosis.