ANDEAN HIGH-ALTITUDE ANCESTRY DOES NOT PROTECT FROM ACUTE MOUNTAIN SICKNESS AND ALTITUDE-INDUCED ARTERIAL HYPOXEMIA

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SUMMARY

It is thought that adaptive changes protect high-altitude populations against altitude-induced diseases, but information from well controlled studies is lacking. In a prospective, controlled study, we assessed the prevalence of acute mountain sickness (AMS) and severity of altitude-induced arterial hypoxemia in non-acclimatized Aymara and non- Aymara children and adolescents during the first 48h after rapid ascent by bus from sea level to 3500masl. To exclude confounding protective effects conferred by developmental changes induced by being born or living at high altitude, only children and adolescents who were born and had been permanently living at sea level were included. In 91 healthy non-acclimatized Chilean children and adolescents (37 with Aymara high-altitude ancestry, 54 non-Aymaras), we assessed for AMS (Lake Louise scoring system) 6, 18 and 42h after a 2.5h ascent by bus to a high-altitude research station located at 3500masl. The overall prevalence of AMS (Aymaras, 22 of 37, 59%; non-Aymaras (39 of 54, 72%; p=0.26) and the severity of AMS (Aymaras, mean score 4.7, non-Aymaras, mean score 4.6, p=0.72) and altitude-induced arterial hypoxemia (82.9 vs 82.5%, p=0.73) were comparable in the two groups. These findings provide the first evidence that Andean high-altitude ancestry per se does not decrease significantly the prevalence of AMS and severity of altitude-induced arterial hypoxemia in children and adolescents, suggesting that in Andean populations evolutionary adaptation itself does not confer important protection against these frequent problems.

Introduction

High altitude hypoxia represents a unique environmental stressor that in altitude populations may lead to adaptive changes which attenuate altitude-induced alterations of homeostasis and confer protection against altitude-induced diseases (Beall, 2006; MacInnis *et al.*, 2010). In high-altitude populations, this ability to adapt could be related genetic factors acquired during evolutionary adaptation and/or to changes ocurred during foetal development and growth (Brutsaert *et al.*, 2004). Travel to highaltitude destinations above 2500masl for recreational motifs exposes several hundred thousands of non-acclimatized tourists to arterial hypoxemia and related medical risks. Acute mountain sickness (AMS), a syndrome of nonspecific symptoms including headache, fatigue, anorexia and nausea, dizziness, and sleep disturbance, is by far the most frequent problem (Imray *et al.*, 2010). While there is general agreement that speed of ascent, absolute altitude, and prior acclimatization are determinants of AMS susceptibility, genetic factors may also play an important role (MacInnis *et al.*, 2010).

We speculated that adaptive mechanisms protect Aymara children and adolescents against AMS and altitude-induced hypoxemia compared to non-Aymara children and adolescents. To eliminate the potentially important confounding protective effects related to developmental changes induced by being born and/or living at high altitude, we studied children and adolescents of highland ancestry who were born and had been permanently living at sea level. In a prospective and controlled study, we assessed the prevalence of AMS and measured arterial oxygen saturation during the first 48h after rapid ascent by bus from sea level to 3500masl in non-acclimatized Aymara and non-Aymara children and adolescents born and permanently living at sea level.

Materials and Methods

Study group

Between March and August 2012, we studied 91 healthy Chilean children and adolescents who were born and had been permanently living at sea level. Of the participants, 37 were Aymaras (13.9-17.7 years old, 18 girls and 19 boys) and 54 were non-Aymaras (13.7-17.5 years old,

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LA ASCENDENCIA ANDINA DE GRAN ALTITUD NO PROTEGE CONTRA EL MAL AGUDO DE MONTAÑA NI LA HIPOXEMIA ARTERIAL INDUCIDA POR LA ALTITUD

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RESUMEN

Se cree que cambios adaptativos protegen a las poblaciones de gran altitud contra enfermedades inducidas por la altitud, pero no existe información de estudios bien controlados. En un estudio prospectivo, controlado, evaluamos la prevalencia del mal agudo de montaña (AMS) y la gravedad de la hipoxemia arterial inducida por la altitud, en niños y adolescentes de ascendencia aymara y no-aymara, no aclimatados, durante las primeras 48h tras un rápido ascenso en autobús desde el nivel del mar hasta 3500msnm. Para excluir confusión de efectos protectores conferidos por cambios evolutivos inducidos por haber nacido o vivido a gran altitud, solo se incluyó niños y adolescentes que habían nacido y vivido permanentemente al nivel del mar. En 91 niños y adolescentes (37 de ascendencia aymara de gran altitud y 54 de ascendencia no-aymara) se evaluó el AMS (Lake Louise scoring system) 6, 18 y 42h después de subir a 3500msnm. La prevalencia global (aymaras, 22 de 37, 59%; no-aymaras, 39 de 54, 72%; p=0,26) y la gravedad (aymaras, puntuación promedio de 4,7; no-aymaras, puntuación promedio 4,6; p=0,72) de la AMS, y la hipoxemia arterial inducida por la altitud (82,9 vs 82,5%, p=0,73) fueron semejantes en ambos grupos. Estos resultados proporcionan la primera evidencia de que la ascendencia andina de gran altitud per se no disminuye significativamente la prevalencia de la AMS ni la gravedad de la hipoxemia arterial inducida por la altitud en niños y adolescentes, sugiriendo que la adaptación evolutiva en poblaciones andinas no confiere una importante protección contra estos frecuentes problemas.

ASCENDÊNCIA ANDINA DE ALTA ALTITUDE NÃO PROTEGER DA MAL AGUDO DE MONTANHA E HIPOXEMIA ARTERIAL INDUCIDA PELA ALTITUDE

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RESUMO

Pensa-se que mudanças adaptativas proteger as populações de alta altitude contra induzida altitude-doenças, mas não existe qualquer informação a partir de um estudo controlado. Em um estudo prospectivo, controlado, avaliou-se a prevalência de doença aguda montanha (AMS) e gravidade da induzida por altitude hipoxemia arterial em não aclimatado Aymara e as crianças e adolescentes no-Aymara durante as primeiras 48h após a subida rápida de ônibus do nível do mar até 3500msnm. Para excluir confundindo efeitos protetores conferidos por mudanças no desenvolvimento induzidas por ter nascido ou viver em altitude elevada, apenas as crianças e adolescentes que nasceram e tinham sido permanentemente vivem ao nível do mar foram envolvidas. Em 91 crianças e adolescentes (37 com ascendência Aymara de grande altitude, 54 no-Aymaras), foram avaliados para AMS (Lake Louise scoring system) 6, 18 e 42h após uma subida em 3500msnm. A prevalência geral de AMS (Aymaras, 22 de 37, 59%; no-Aymaras (39 de 54, 72%; P=0,26) e da gravidade da AMS (Aymaras, pontuação média de 4,7, no-Aymaras, a média de pontuação de 4,6; p=0,72) e hipoxemia arterial induzida pela altitude (82,9 vs 82,5%; p=0,73) foram comparáveis nos 2 grupos. Estes resultados fornecem a primeira evidência de que ascendência andina de grande altitude per se não diminui significativamente a prevalência do AMS e gravidade da hipoxemia arterial induzida pela altitude em crianças e adolescentes, sugerindo que, em populações andinas a própria adaptação evolutiva não confere protecção importante contra esses freqüentes problemas.

26 girls and 28 boys). Participants were considered Aymaras if both grandfathers and both grandmothers had family names of Aymara origin, as Fuentes *et al*. (2014) have shown, based on ancestry-informative marker (AIM) estimates, that individuals with two Aymara surnames in our study region (Arica-Parinacota region in Northern Chile) harbor on average 99.68 ±0.49% of American genetic background. None of the participants had slept at high altitude (>2500m) during the last six months prior to the study, and none was taking any medication during the study. The experimental protocol was approved by the review board on human investigation of the University of Tarapacá and all parents provided written informed consent.

Based on data published by Moraga *et al.* (2008) assuming that a difference of 50% in the prevalence of AMS between Aymara and non-Aymara participants would be clinically relevant, and considering an alpha error of 5% and a desired statistical power of 90%, we calculated that the minimal sample size of each group should be n=30 to test our hypothesis. With regard to arterial oxygen saturation (SaO2) assuming an SaO2 of 82.2 ±3.2% on the day of arrival in non-Aymara and a 3% higher value in Aymaras to be clinically significant, and considering an alpha error of 5% and a desired statistical power of 90%, we calculated that the minimal sample size of each group should be n=25 to test our hypothesis.

The participants ascended in mixed groups (n=10-50) of Aymaras and non-Aymaras with a 2.5h bus ride that took them from sea level (Arica, Chile) to the high-altitude research station at 3500masl (Putre, Chile), where they arrived in the early afternoon. They then spent two days and two nights at the research station. During the stay, all participants received the same diet and care was taken to assure an adequate fluid intake. Physical activity was standardized. On the day of arrival, the participants rested quietly and visited the village of Putre. On the second day, participants were offered the possibility to participate in recreational activities of moderate physical intensity. On the morning before descent the participants

remained within the research station.

Evaluation for acute mountain sickness (AMS)

The presence of AMS was assessed on the evening of the day of arrival and on the two following mornings (i.e. 6, 18 and 42h after arrival at high altitude) with a Spanish version of the Lake Louise self-assessment questionnaire (Imray *et al*., 2010) under the supervision of a trained examiner, as described previously (Bloch *et al*., 2009; Rexhaj *et al*., 2011). Briefly, for each of the five items (headache, gastrointestinal symptoms, fatigue, dizziness and sleep disturbance), the participants noted a score between 0 and 3, with 0 indicating the absence of the symptom; 1, mild symptoms; 2, moderate symptoms; and 3, severe, incapacitating symptoms. Participants were considered suffering from AMS if they were experiencing headache (score ≥1), the condition *sine qua non* for the diagnosis of AMS, and the total score on the self-assessment questionnaire was ≥3, the maximal score for the questionnaire being 15 (Imray *et al*., 2010). After the assessment, participants with AMS suffering from headache were treated with acetaminophen, if needed.

Measurement of arterial oxygen saturation

Trans-cutaneous arterial saturation and heart rate were measured at a fingertip with a pulse oxymeter (OxiMax®N-595, Nellcor, Pleasantn, CA) before each evaluation for AMS.

Statistical analysis

Statistical analysis was done with the Graphpad Prism 5 software package (GraphPad Software Inc, San Diego, CA, USA). Unpaired 2-tailed t tests were used for group comparisons of continuous variables. For comparisons of categorical variables the Fischer exact test was used. Data are expressed as mean with standard deviation (SD). A p value <0.05 was considered to indicate statistical significance.

Results

All participants completed the daily AMS questionnaires. Table I shows the mean and standard deviation (SD) of the age, weight, height and body mass index (BMI) of the participants. It can be seen that there are no significant differences between the Aymaras and non-Aymaras children and adolescents in the study.

At low altitude, the AMS score was equal to 0 in all participants.

Figure 1 shows that in both Aymaras and non-Aymaras, the large majority of cases (roughly 80%) of AMS developed during the first 6h at high altitude and that the total prevalence of AMS, as well its prevalence at the three time points of the study, was not statistically different (all p's >0.09) between Aymaras and non-Aymaras. On the evening of the day of arrival (i.e. 6h after arrival at high altitude), 18 of the 37 Aymaras (49%) and 31 of the 54 non-Aymaras (57%) (p=0.52, Aymaras *vs* non-Aymaras) suffered from headache (the *conditio sine qua non* for the diagnosis of AMS) and had a symptom score greater or equal to 3 (range 3 to 9). On the morning of the next day (18h after arrival at high altitude) AMS had resolved for 10 of the 18 Aymaras and for 11 of the 31 non-Aymaras suffering from AMS on the evening of the first day, and new AMS developed in 4 Aymaras and 8 non-Aymaras (range of scores 3 to 9), resulting in 12 Aymaras (32%) and 28 non-Aymaras (52%) suffering from AMS at this time point. During the next 24h at high altitude, the prevalence of AMS decreased markedly in both groups, such that on the morning of the third day at high altitude (42h after arrival), only 7 (19%) Aymaras and 12 (23%) non-Aymaras had symptoms of AMS (range of scores 3 to 7).

The overall prevalence of AMS among the participants was 67% (61/91). In 50% (30 of 61) of the participants suffering from AMS, the symptoms lasted for less than 24h. In 46 subjects the symptoms disappeared spontaneously, whereas the remaining 15 were given acetaminophen for headache. Of the 15 participants receiving drug treatment, 13 (6 Aymaras, 7 non-Aymaras) were treated 6h after arrival at high altitude. The symptoms responded rapidly to this symptomatic treatment.

Throughout the study, arterial oxygen saturation was similar in Aymaras and non-Aymaras (Table II) it was also not different between the participants who suffered from AMS and those who did not: 6h (82.8 (SD 4.9) *vs* 82.7% (4.5), p=0.97), 18h (86.9 (4.1) *vs* 87.6% (3.1), p=0.41) and 42h (89.3 (3.40) *vs* 89.9% (2.5), p=0.41).

Among the participants who suffered from AMS, the disease was mild and comparable in the two groups; for a theoretically maximal score of 15, the mean Lake Louise score was 4.7 (SD 1.8) in Aymaras and 4.6 (1.7) in non-Aymaras (p=0.72 Aymaras *vs* non-Aymaras). There was no difference in the severity of the symptoms between the two genders (mean Lake Louise score 4.6 (1.7) in girls, and 4.7 (1.5) in boys, p= 0.84 girls *vs* boys) and there existed no significant differences in the frequency of the symptoms making up for AMS between Aymaras and non-Aymaras.

TABLE I
MEAN AND STANDARD DEVIATION (SD) OF AGE, WEIGH AND BODY MASS INDEX (BMI) OF THE PARTICIPANTS

	Aymara mean (SD) (n=37)	Non-Aymara mean (SD) (n=54)	Sig. p
Age (years)	14.8 (0.7)	14.8 (0.6)	1.0
Weight (kg)	63.5 (11.9)	63.5 (14.8)	0.99
Stature (cm)	160.0 (7.8)	164 (8.3)	0.40
BMI ($kg \cdot m^{-2}$)	24.7 (3.7)	23.2 (4.0)	0.16

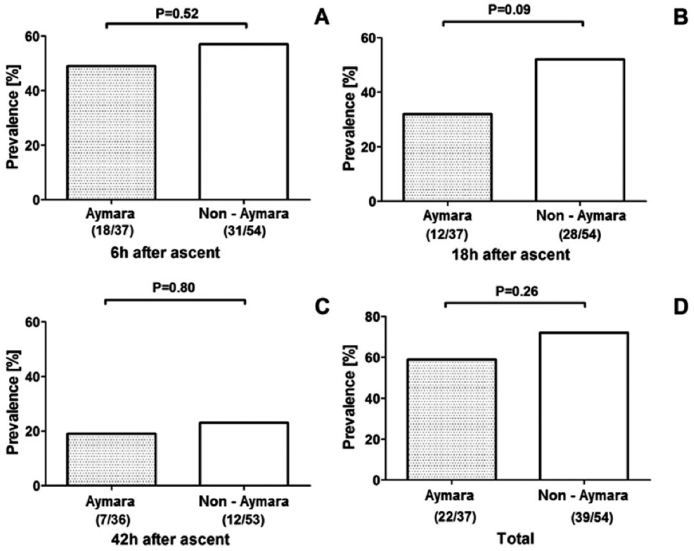

Figure 1. Day-to day (6, 18, and 42h after arrival, panel A, B, and C, respectively) and total prevalence (panel D) of acute mountain sickness (AMS) in non-acclimatized Aymara (n=37, hatched bars) and non-Aymara (n=54, open bars) children and adolescents born and permanently living at sea level after rapid ascent by bus to 3500masl.

Discussion

AMS is a major health problem typically occurring shortly after arrival at high altitude

TABLE II
ARTERIAL OXYGEN SATURATION IN AYMARAS AND NON-AYMARAS AT SEA LEVEL AND IN THE HEIGHT

Time (h)	Height (masl)	Aymara		Non-Aymara		
		n	SaO2 % (SD)	n	SaO2 % (SD)	Sig p
0	20	37	98.1 (1.5)	54	98.4 (0.6)	0.15
6	3500	37	82.9 (4.1)	54	82.5 (5.2)	0.73
18	3500	37	87.9 (3.2)	54	86.6 (4.2)	0.13
42	3500	36	89.7 (4.5)	53	89.3 (2.9)	0.64

(Hackett and Roach, 2001; Bloch *et al.*, 2009). While speed of ascent and absolute altitude are established determinants of its occurrence (Hackett and Roach, 2001; Imray *et al.*, 2010), high altitude ancestry, by protecting against this problem, has also been suggested to play a role (Beall, 2000; MacInnis *et al.*, 2010), but there is no information from controlled studies. This is the first controlled prospective study to examine the effects of adaptive changes related to Andean high altitude ancestry *per se*, on altitude-induced arterial hypoxemia and the prevalence, time-course and severity of AMS. The main new finding was that both the prevalence and severity of AMS, and the altitude-induced arterial hypoxemia during the first 3 days after rapid ascent to 3500m, were not different between non-acclimatized Aymara and non-Aymara children and adolescents who were born and had been permanently living at sea level. These findings strongly suggest that Andean high altitude ancestry does not confer important protection against altitude-induced hypoxemia and AMS, the most frequent altitude related medical problem.

An important feature of the present study was that all participants were born and had been permanently living at low altitude. This allowed to rule out the potentially important confounding protective effects conferred by developmental changes induced by being born and/or by living at high altitude, and to study exclusively the protective effects conferred by adaptive changes related to high altitude ancestry. We found that Aymara high altitude ancestry had no significant effect on AMS prevalence or severity at any of the three time points of the study. Recent controlled studies of the prevalence and severity of AMS in non-acclimatized European children in the Alps (Bloch *et al.*, 2009; Rexhaj *et al.*, 2011) using similar speed of ascent, absolute altitude and time of observation allow some additional comparisons. First, the prevalence of AMS (total prevalence between 15 and 38%) in European children of similar age was similar (or tended to be lower) to the one observed in Aymara children in the present study, strengthening the interpretation that Aymaras do not appear to be protected from this problem. Second, the overall and day-to-day prevalence of AMS in these European children was significantly lower than the one observed in non-Aymara children in the present study, indicating that the inability to demonstrate a protective effect of Aymara ancestry against AMS in the present studies does not appear to be related to an unexpectedly low prevalence of this problem in the non-Aymara controls. Third, this controlled study allowed to exclude the influence of confounding factors known to facilitate AMS, such as exercise (Roach *et al.*, 2000). Taken together, these comparisons further strengthen the conclusion that Aymara high altitude ancestry *per se* does not confer protection against AMS. In line with this interpretation, we found that Aymara ancestry also did not attenuate the altitude-induced decrease of arterial oxygenation, since arterial oxygen saturation was comparable in the two groups. Finally, it is likely that the present findings in Aymaras also are valid for Quechuas, the other Andean high altitude population, since there is evidence that genes facilitating high altitude adaptation are better preserved in the former (Gaya-Vidal *et al.*, 2011). Further study is needed to examine whether Tibetan or Ethiopian high-altitude ancestry that may have resulted in adaptive changes distinct from those in Andean high altitude populations (Beall, 2000; MacInnis *et al.*, 2010) also does not confer such protection. Observational data comparing AMS prevalence in adult Tibetans and Han Chinese suggest that in adults, Tibetan ancestry may have a protective effect (Li *et al.*, 2011).

The time course of AMS was also comparable in the two groups, and, as in previous studies (Bloch *et al.*, 2009; Rexhaj *et al.*, 2011), the majority of cases of AMS developed during the first 6h after arrival at high altitude. Moreover, in line with previous findings in children at a similar study altitude in the Alps (Bloch *et al.*, 2009; Rexhaj *et al.*, 2011) the disease was relatively mild (mean symptom score 4.7 and 4.6, of a theoretical maximum of 15, in Aymaras and Europeans respectively) and symptoms resolved rapidly, in the majority of cases spontaneously, in the remaining after administration of symptomatic treatment. None of the participants needed to be evacuated to low altitude and in none AMS progressed to life-threatening high-altitude cerebral or pulmonary oedema (Hackett and Roach, 2001; Sartori *et al.*, 2010; Scherrer *et al.*, 2010). Collectively, these observations suggest that rapid ascent of non-acclimatized healthy young persons to this study altitude appears to be safe, since it rarely induces these life-threatening medical complications.

In the present study, we used surname analysis of both grand-parents as a proxy of genetic ancestry in Aymara participants and did not assess potential European admixture by assessing genetic markers. Recent data using ancestry informative markers to estimate individual genetic ancestry suggest that in northern Chile altitude ancestral assessment based on Aymara surnames appears surprisingly reliable (Fuentes *et al.*, 2014; Rothhammer *et al.*, 2015). In line with these observations, in Peruvian Quechuas born at sea level, European admixture assessed by ancestry-informative genetic markers was low (<10%) and had no detectable effect on the exercise phenotype during acute high altitude exposure (Brutsaert *et al.*, 2004); most interestingly, this study found that Quechuas born and raised at high altitude had better exercise performances than their sea level counterparts, emphasizing the importance of environmental developmental adaptation to high altitude rather than evolutionary genetic adaptation in this setting.

Conclusion

In conclusion, here we show for the very first time that evolutionary adaptive changes related to Aymara high-altitude ancestry *per se* do not confer protection against acute mountain sickness and altitude-induced arterial hypoxemia during rapid exposure to 3500masl.

Disclosures

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