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Original Article

Is restless legs syndrome associated with chronic mountain sickness?

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ABSTRACT

Background: Restless legs syndrome (RLS) and chronic mountain sickness (CMS) share physiological traits. Our objective was to explore a possible association between RLS and CMS.
Methods: We carried a cross-sectional study with male subjects living between 4100 and 4300 m above sea level. Participants underwent a clinical interview, physical examination, electrocardiographic (EKG) recording, and spirometry. We classified subjects into CMS, Limbo, and healthy high-altitude dwellers (hHAD), according to their Quinghai score and hematocrit levels. We applied the "Paradigm of questions for epidemiological studies of RLS," The International Restless Leg Syndrome Study Group Scale, and the Pittsburgh Sleep Quality Index. Logistic regression analysis was used to determine the association between variables.
Results: Seventy-eight male subjects were included. Forty subjects were hHAD, 23 were CMS patients, and 15 participants were considered as Limbo. CMS and Limbo subjects had a higher frequency of RLS ($p < 0.05$). Limbo subjects had the highest severity score for RLS. There were no differences in age, body mass index (BMI), or tobacco use between RLS patients and non-sufferers. In the multivariate analysis, CMS was not associated with RLS diagnosis. Oxygen saturation ($p = 0.019$), poor sleep quality ($p < 0.01$), and Quinghai score of ≥6 ($p = 0.026$) were independently associated with RLS diagnosis.
Conclusions: Our results did not show a direct association between RLS and CMS; however, RLS was associated with reduced oxygen saturation. Hence, RLS could represent an early clinical manifestation of hypoxia, or, in CMS natural history, an early sign of maladaptation to high altitude.

1. Introduction

Willis–Ekbom disease or restless leg syndrome (RLS) is a sensorimotor disorder that manifests at rest. Its distinctive characteristic is the presence of unpleasant leg perceptions accompanied by an intense desire to move the limbs, and they are not solely accounted for as symptoms primary to another medical or behavioral condition [1]. RLS has been linked to iron deficiency [2,3] and dopamine alterations. Hypoxia in the limbs has recently been found to be a key factor involved in the pathology of this disease [4,5].

Monge's disease or chronic mountain sickness (CMS) is a progressively incapacitating disease characterized by excessive erythrocytosis and chronic hypoxemia [6,7] that arises from the loss of adaptation to high altitude, and it subsequently leads to heart failure and hypercoagulability [8]. It can also be associated with pulmonary hypertension [8]. CMS is an important public health problem for Andean countries, where it affects between 5% and 18% of high-altitude dwellers (HAD) living 3200 m above sea level [9–11].

It has been reported that healthy Andean males present higher hemoglobin, compared to healthy Tibetan males; the latter group is considered to be well adapted to high altitude [12]. Furthermore, the Andean population has a higher prevalence of CMS compared to the Tibetan population [13].

Both CMS and RLS share oxygen alteration as a common trait. Additionally, dopamine synthesis may be altered in hypobaric hypoxia, characteristic of high altitudes [14,15], and a higher prevalence of RLS in high-altitude regions compared to coastal areas has been reported [16]. We conducted a cross-sectional study to explore a possible association between RLS and CMS.

Abbreviations: hHAD, healthy high-altitude dwellers; IRLSSG, International Restless Leg Syndrome Study Group; PSQI, Pittsburgh Sleep Quality Index.

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2. Methods

This study forms part of a larger prospective research project that aims to evaluate a possible association between obstructive sleep apnea and CMS.

2.1. Patient recruitment

We recruited subjects from five cities located between 4100 and 4300 m above sea level, in the province of Pasco, Peru (Rancas, Carhuamayo, Quiulacocha, Cerro de Pasco and Yurajhuanca). This region's economy is diverse, driven by extensive mining activity. Recruitment was carried out in the setting of a health-care campaign aimed at screening for excessive erythrocytosis. Radiobroadcasting and flyers were used for advertising; RLS symptoms were not mentioned through this media.

Male subjects between 18 and 70 years old, permanently living at high altitude (>3000 m above sea level), without previous diagnosis of RLS, and who signed written informed consent, were included in the study. Patients were excluded if they presented chronic pulmonary disease, cardiovascular disease, history of mining activity with abnormal spirometry, history of smoking with abnormal spirometry, drank more than two alcoholic beverages per day, had recently traveled to low-altitude environments (<3000 m above sea level for a total of seven days in the last six months), had a phlebotomy, or suffered from leg cramps.

2.2. Clinical evaluation and ancillary analysis

The hematocrit was determined with the micro-hematocrit method; two samples were attained, and the readings were averaged. A complete electrocardiography (EKG) was obtained with a standard arrangement of electrodes. A spirometry was obtained using a Cosmed® desktop spirometer (Italy). Two expiratory maneuvers were performed, and the best one was registered. Oxygen saturation was determined through pulse oximetry in the index finger of the right hand.

All patients underwent a short clinical interview and a physical examination by a research physician; vital signs and basic anthropomorphic measurements were gathered. Relevant epidemiological and clinical information, including history of allergies or psychiatric illness that could deserve medical treatment, was collected through a questionnaire. Both records and ancillary examinations were used to diagnose pulmonary or cardiovascular disease that would justify the exclusion of the subjects.

2.3. Questionnaires

The Quinghai CMS score was developed for the diagnosis of CMS rated from 0 to 24. It consists of seven symptoms (breathlessness or palpitations, sleep disturbance, cyanosis, dilatation of veins, paresthesias, headache, and tinnitus), and hemoglobin. A score [6] over five points was considered positive. CMS was diagnosed with a positive Qinghai score and a hematocrit of ≥63%. Healthy HAD (hHAD) were selected with a negative Qinghai score and a hematocrit of ≤52%, according to normal values established in previous studies for Andean populations [17]. Subjects with a hematocrit of >52% but <63% were considered as Limbo.

Subsequently, the Pittsburgh Sleep Quality index (PSQI), validated in Spanish, was employed to assess sleep quality and sleep latency. A value >5 was defined as poor sleep quality [18]. Sleep medication was evaluated through the sixth item of the questionnaire.

Finally, RLS was diagnosed with the Spanish-validated version of the "Paradigm of questions for epidemiological studies of RLS" [19]. The International Restless Leg Syndrome Study Group (IRLSSG) scale was applied for severity [20]. We classified patients according to RLS diagnosis.

2.4. Statistical analysis

Continuous variables were expressed as mean and standard deviation, or medians and 25–75th percentiles; categorical variables were reported as percentages. Analysis of nominal variables was performed through Fisher's exact test. Student's *t*-test or Mann–Whitney *U*-test was used for analysis between continuous and nominal variables.

Variables significantly associated with RLS diagnosis in univariate analysis were included for multivariate analysis, using logistic regression to predict RLS diagnosis. Age was also included in the models, due to its clinical relevance in RLS. Separate regression models were built with positive Quinghai score and CMS diagnosis due to collinearity between variables.

A post hoc analysis of the relationship between RLS diagnosis and hematocrit was performed. We categorized subjects into three groups according to their hematocrit value. The cutoff value of hematocrit (48%) was established taking into consideration the normal values for the Peruvian population at sea level [21] and the cutoff point for excessive erythrocytosis.

A value of $p < 0.05$ was considered to be statistically significant. STATA 10.0 was used for statistical analysis.

2.5. Ethical approval

Participants signed written informed consent. The study was reviewed and approved by the ethics committee of the "Universidad Peruana Cayetano Heredia" – Lima, Peru.

3. Results

Seventy-eight male adult patients were eligible, consented to participate, and underwent evaluation. Twenty-three subjects were diagnosed with CMS, 40 subjects were classified as hHAD, and 15 participants were considered as Limbo.

CMS subjects were significantly older, and they had a higher BMI than hHAD. CMS had a significantly lower oxygen saturation than Limbo and hHAD. RLS diagnosis was more frequent in CMS and Limbo subjects. A higher severity score of RLS was found only in Limbo subjects (Table 1).

In the CMS (+) group, subjects with RLS differ from those without RLS only in the PSQI score ($p = 0.004$). In the hHAD group, the RLS

Table 1
Subject characteristics according to CMS status.

	CMS (+)	Limbo	hHAD
	n = 23	n = 15	n = 40
Age[a,*]	46 (39–53)	38 (27–49)	31 (23.5–51.5)
BMI[a,*]	26 (24–30)	24.5 (23–29)	24 (22–26)
Mining history[b]	9%	8%	13%
Heart Rate[a,*]	76 (68–80)	68 (62–75)	69 (61–75)
Syst BP[a]	110 (100–120)	110 (90–110)	110 (100–117.5)
Diast BP[a]	80 (70–80)	70 (60–70)	70 (60–80)
Tabaco[b]	4%	0%	8%
Hto[a,*,†,‡]	68 (65–75)	54 (50–62)	50 (47–51)
SpO2[a,*,†]	86 (80–93)	89 (85–92)	92 (89–94)
RLS[b,*,‡]	43%	47%	13%
Severity score[a,‡]	16 (0–22)	20.5 (17.5–24)	0 (0–15)
PSQI score[a]	5 (4–7)	7 (4–9)	5 (3–8)

[a] Mann–Whitney *U*-test. [b] Fisher's exact test.* $p < 0.05$ CMS versus hHAD; † $p < 0.05$ CMS versus Limbo; ‡ $p < 0.05$ Limbo versus hHAD.
CMS (+), Chronic Mountain Sickness; Limbo, Subjects with a hematocrit >52% but <63%; hHAD, healthy high-altitude dwellers.