Prevalence of Willis–Ekbom disease in rural coastal Ecuador. A two-phase, door-to-door, population-based survey

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ABSTRACT

Objective: To estimate the prevalence of Willis–Ekbom disease (WED) in a racially homogeneous population of adults Amerindians living in rural coastal Ecuador, and to assess the reliability of the International Restless Legs Syndrome Study Group (IRLSSG) questionnaire when used in population-based studies.
Methods: Two-phase, door-to-door, population-based survey. During Phase I, rural doctors screened all Atahualpa residents aged ≥40 years with the IRLSSG questionnaire. In Phase II, neurologists evaluated suspected WED cases and a matched sample of negative individuals.
Results: The census identified 665 persons aged ≥40 years. An affirmative response to the questionnaire was obtained in 94 persons. Medical history and neurological examination confirmed the diagnosis of WED in 40 of them. The evaluation of 188 non-suspected individuals revealed no further cases. The questionnaire had a sensitivity of 100% (95% CI, 89% to 100%), a specificity of 78% (95% CI, 72% to 83%), a positive predictive value of 0.43 (95% CI, 0.33 to 0.53), and a negative predictive value of 1 (95% CI, 0.98 to 1). The prevalence of WED in Atahualpa residents aged ≥40 years was 6%.
Conclusion: The prevalence of WED in this adult Ecuadorian population is higher than that reported from most studies conducted in tropical countries, but similar to that found in Brazil. Specificity and positive predictive value of the IRLSSG questionnaire are poor, which reinforces the need for a second phase that should include an expert interview.

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1. Introduction

Willis–Ekbom disease (WED), also known as restless legs syndrome, is a disorder of unknown etiology that is characterized by four fundamental criteria: a) an urge to move the legs usually but not always accompanied by leg sensations, b) symptoms get worse later in the day or at night, c) symptoms are worse at rest, i.e., sitting or lying, and d) symptom experience at least partial or temporally relief by activity while the activity is actually occurring [1]. WED has been categorized as both a sleep disorder and a movement disorder, and some have even proposed that symptoms may be generated in the peripheral nervous system [2–4]. Such controversies are partially related to the lack of consensus on the pathophysiological mechanisms implicated in the genesis of WED. Theories explaining this condition include, among others, an imbalance between thyroid hormones and the dopaminergic system [5], increased thalamic release of glutamate associated with dopaminergic abnormalities [6], altered control of iron homeostasis [7], and even immune-related mechanisms [8]. Irrespective of the diversity of these hypotheses, there seems to be a central role of the dopaminergic system in the pathogenesis of WED that is confirmed by the therapeutic response to dopamine agonists [9].

The burden of this condition may be related to latitude, a fact that has been corroborated in reviews of epidemiologic surveys showing that WED is more prevalent in template regions away from the Equator than in the Tropics [10,11]. Initial population-based studies from tropical regions suggested a very low prevalence of WED that ranged from 0.01% to 3.2% [12–16]. More recently, a single study from Brazil showed a 6.4% prevalence of WED [17], which is still low, but is more in accordance with that reported from some Western and Southern populations. Race/ethnicity – as a factor influencing prevalence – has not been considered in these studies. A study conducted in the Southwestern US revealed that, beyond race, the acculturation of Hispanics of

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Mexican origin was an independent risk factor for a higher WED prevalence [18]. So, if race/ethnicity is going to be considered as a factor influencing WED prevalence, racially homogeneous populations need to be studied in their natural habitats to reduce biases of migration or acculturation.

The aim of the present study is to estimate the prevalence of WED in a racially homogeneous population of Amerindians living very close to the Equator, and to assess the reliability of the most commonly used field instrument for diagnosing WED in population-based studies.

2. Methods

2.1. Population studied

Atahualpa is located at the sea level, 10 miles West of the Pacific Ocean (2°18′S, 80°46′W) and was selected for this study as it is representative of the rural villages of coastal Ecuador regarding weather conditions, race/ethnicity, and lifestyles. The weather is hot and dry, with 12 daily hours of sunlight all over the year, and scarce rains from January through April. Inhabitants do not migrate, and a sizable proportion of them have never visited large urban centers, which are more than 100 km apart. More than 95% of the population belongs to the Ecuadorian Native/Mestizo ethnic group (Amerindians). Four surnames – all of Spaniard origin – account for more than 50% of the population. This does not mean crossbreeding or consanguinity, since it was common for ancient natives to adopt the surnames of their Spaniard conquerors, and there is historical evidence that the village already existed by the time Spaniards arrived to Ecuador. Phenotypically, these persons have an olive-moderate brown skin (Type IV in the Fitzpatrick scale [19], dark brown eyes and hair, and are of short stature (mean height of the adult population in a previous study was 149 ± 10 cm [20]).

2.2. Study design

The Atahualpa Project is a multi-step, population-based, study, designed to reduce the burden of cardiovascular and neurological diseases of adults living in rural coastal Ecuador [21–23]. The protocol and the informed consent form were approved by the IRB of Hospital-Clínica Kennedy, Guayaquil — Ecuador (FWA 00006867). For this part of the study, trained rural doctors performed a door-to-door survey directed to assess demographic characteristics of all Atahualpa residents aged ≥40 years, defined as those persons who had lived in the community for three months before the prevalence day (June 15, 2013). During the survey (*Phase I*), consented individuals were directly interviewed by rural doctors with a questionnaire directed to identify those with suspected WED. The field instrument was that developed by the International Restless Legs Syndrome Study Group (IRLSSG) in 2003 to be used in epidemiologic studies [24], and subsequently validated in Ecuadorian Spanish-speaking communities [13]. It consists of four questions and the first three of them have to be answered affirmatively to make an individual suspicious (Table 1).

In *Phase II*, a certified neurologist (O.H.D.) and a sleep specialist (P.R.C.) examined all individuals who screened as suspected cases of WED. In addition, a sample of individuals who were considered negative during the screening phase also underwent a complete interview and a neurological examination to assess for possible false negative cases during the survey. We selected two negative individuals matched by age and gender for each positive case. Neurologists were blinded as to whether the individual was a suspected case or a negative control. Specialists used the four essential criteria that have to be met for diagnosing WED, according to the IRLSSG [24]. During this phase of the study, persons with a definitive diagnosis of WED were also inquired about age of onset, medications used for this disorder, relation with pregnancy (in women), and disease severity. The latter was assessed by the use of the IRLSSG rating scale [25]. This scale consists of 10 questions rated on a four point Likert scale with a maximum total score of 40; a score >20 is considered a severe case of WED. As this scale was originally written in English, it was independently translated and back-translated from its original version to Spanish by bilingual physicians from our group (O.H.D., P.R.C.). Then, the Spanish version of the IRLSSG severity scale was culturally adapted – including vernacular Spanish words used by local people – with the aid of Atahualpa's community leaders and rural doctors that had been working in the village, and tested in a random sample of the population before the study. Finally, we asked for family history of symptoms of WED in first- and second-degree relatives; as some of those persons also live in Atahualpa, we reviewed our files to see if they have been included as suspicious cases (during *Phase I*), and if not, we visited them at their houses for further verification.

2.3. Statistical analyses

The reliability of the field instrument used during *Phase I* was assessed by calculating its sensitivity and specificity, as well as its positive and negative predictive values (using numbers of true and false positive suspected cases, and those of true and false negative controls). Descriptive statistics are presented as means with standard deviations for continuous variables and as percentages for categorical variables. Differences on demographic characteristics across persons with and without RLS were tested by the use of the χ^2 test for categorical variables and by ANOVA for continuous variables. The analysis of data was carried out using SPSS18 (SPSS Inc., Chicago, Illinois, USA) software. Differences are considered significant if $p < 0.05$.

3. Results

The census identified a total of 688 Atahualpa residents aged ≥40 years, of whom 23 refused to participate. Therefore, 665 persons (mean age, 59.5 ± 12.6 years; 58% women) were interviewed with the IRLSSG instrument for the detection of symptoms consistent with WED. The questionnaire was positive in 94 persons (14%). Expert clinical interview and neurological evaluation showed that only 40 of these suspected persons had WED. Nineteen of the 54 false positive cases had chronic knee arthritis as the cause of the symptoms, 12 had nocturnal cramps, 10 had painful peripheral neuropathy, eight had peripheral artery disease, and the remaining five had non-specific complains that could not be categorized as a specific WED-mimic disorder. In addition, the examination of 188 non-suspected individuals disclosed no further cases of WED.

Table 1
Questionnaire used for identifying persons with suspected Willis–Ekbom disease in the present study (Original English version with Spanish translation). According to the 2003 position paper of the International Restless Legs Syndrome Study Group, the first three questions have to be positive to make an individual a suspected case [24].

- Do you have unpleasant sensations in your legs combined with an urge or need to move your legs? [*Usted ha tenido molestias o sensaciones desagradables en sus piernas asociadas con la necesidad urgente de moverlas?*]
- Do these feelings (symptoms) occur mainly or only at rest and do they improve with movement? [*Estas molestias o sensaciones desagradables se presentan casi siempre o únicamente cuando usted se encuentra en reposo y mejoran cuando usted se mueve?*]
- Are these feelings (symptoms) worse in the evening or night than in the morning? [*Estas molestias o sensaciones desagradables son peores al final de la tarde o en la noche, comparados con la mañana?*]
- How often do these feelings (symptoms) occur? [*Que tan frecuentemente ocurren estas molestias o sensaciones desagradables?*]