ARIC Manuscript #1053

Manuscript Proposal: (revision)

1. a) Full Title: Racial differences in RLS symptom prevalence and symptom characteristics
   b) Abbreviated Title: Racial differences in RLS prevalence

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3. Timeline: 10/04: Acquire approval from P & P committee and request data set
           11/04: Start date for proposed analysis
           01/05: Start manuscript preparation (anticipated completion by 3/05)

4. Rationale: RLS has been quoted as “the most common and least diagnosed sleep disorder” – a remark based on a recent report suggesting that only 40% of RLS suffers (those who experience symptoms more than twice weekly) report these symptoms to their physicians.(1, 2) Despite growing recognition of Restless Legs Syndrome (RLS) and its impact on sleep, essential features of the disorder remain in question. Although investigators from several RLS centers have proposed that this disorder is more common in Caucasians than in African Americans, no epidemiological studies have assessed prevalence rates of RLS symptoms among African American or other racial/ethnic groups. Available studies on RLS have been based primarily on study samples comprised largely of individuals from European descent demonstrating similar prevalence rates in the range of 7% to 10%, compared to two non-European samples (Singapore and Turkey) with prevalence rates of 0.6% and 3%.(3-8) Such regional differences suggest diversity of RLS expression among various ethnic groups. Racial differences have obvious significance especially in a disorder that may have strong genetic influences. Given that iron deficiency anemia is a strong risk factor for RLS, well-established racial differences in iron metabolism may explain the differential expression of RLS across various racial and ethnic groups.

The Sleep Heart Health Study questionnaire on RLS symptoms provides a unique opportunity to determine racial difference in RLS symptoms by defining the relative frequency and severity of the disorder in a community sample of middle-aged adults. Only one other study has reported frequency and severity of RLS in the general population. Furthermore, there are no available data on whether polysomnographic features are associated with the frequency and severity of RLS in a community sample. Knowing basic sleep indices such as total sleep time, sleep latency, and sleep efficiency could potentially influence treatment and contribute to understanding the relationship of RLS and sleep on quality of life and other comorbid health problems. One area of interest is the finding of two large epidemiological studies demonstrating a higher prevalence of hypertension in RLS than non-RLS sufferers.(9, 10) The aim of this proposal is to evaluate the racial and ethnic differences in the prevalence of RLS symptoms and define relationships between RLS symptoms, sleep quality, and prevalent medical conditions.

Hypothesis 1: Caucasians have a higher prevalence of RLS symptoms than other racial/ethnic groups after adjusting for age and gender.

Hypothesis 2: RLS suffers report shorter sleep time and poorer sleep quality than non-suffers. PSG measures of sleep quality, including total sleep time, sleep latency and wake after sleep will demonstrate more disrupted sleep in RLS suffers and will be related to frequency and severity of RLS symptoms.
Hypothesis 3: RLS sufferers will have a higher prevalence of hypertension after controlling for relevant covariates (e.g., gender, race, BMI, age, smoking).

Hypothesis 4: Individuals with RLS symptoms will have a lower hemoglobin and higher RDW after controlling for relevant covariates (gender, age, smoking).

Study Design: Cross-sectional study to examine the relation between racial/ethnic groups and differences in RLS prevalence.

Population: All subjects participating in the phase II (1999-2003) of the SHHS. Individuals with poor quality sleep studies and ethnic groups with insufficient number of subjects (< 100) will be excluded.

DEPENDENT VARIABLES

RLS diagnosis:

Eight self-report RLS related questions from the Sleep Health Interview Questionnaire (Section C Items 8-15) would be used to establish RLS symptoms and severity. Individuals with RLS symptoms will be grouped according to an aggregate of symptoms compatible with the 4 diagnostic criteria developed by the International Restless Legs Syndrome Study Group (IRLSSG). They will be divided into four groups: Definite RLS, Probable RLS, Possible RLS, and No RLS. The definite category relates to the fact they have all four symptoms in the criteria of RLS rather than a true definite diagnosis.

1) Definite RLS: Individuals who meet all four criteria with positive answers to questions on urge to move, sensory discomfort, onset at rest (and not during activity), relief with walking, and symptoms being worse at night or only present at night or the evening.

2) Probable RLS: From the established criteria, questions on the sensory component and relief with walking are most difficult to ascertain with many individuals reporting positive responses to questions on ‘moving or stretching for relief’. Thus a probable diagnosis will allow for negative or don’t know answers to the questions on sensory discomfort or relief with walking.

3) Possible RLS: Although the urge to move is the salient feature of RLS, several investigators have reported difficulties in acquiring this symptom. A possible diagnosis will allow for a negative response to the question on urge to move but leaving all remaining criteria positive as noted in the definite category.

4) Not RLS: Individuals who fail to meet the criteria as established by the above groups.

RLS Severity:

Two questions in section C of the sleep health interview will be used to establish severity. A RLS severity index will also be calculated by adding the values for each of the two questions based on frequency and intensity of RLS symptoms (Range = 0-9). The number of definite RLS subjects who have more than twice weekly symptoms and report moderate and severely distressing symptoms will determine the prevalence of the “RLS sufferers”.

RLS Onset:
Onset of RLS symptoms will be established by question 15 with early onset at age ≤ 45 years and late onset > 45 years.

**PSG Measures.**

The following data from the polysomnogram will be used: Sleep Latency (SL), Wake After Sleep Onset Time (WASO), Sleep Efficiency (SE), Total Sleep Time (TST), and Sleep Stage Transitions.

**Hypertension:** A previous diagnosis or treatment for hypertension or a SBP ≥ 160 or DBP ≥ 90 during the home visit.

**INDEPENDENT VARIABLES**

**Ethnicity/Race:** We will evaluate differences in RLS groups between White, African American, Hispanic, Asian, and Native Americans.

**Gender/Age:** European studies and the Turkish epidemiological study suggest a 2:1 female to male ratio in early onset females. RLS has also been noted to be more prevalent with older age. Thus, we will determine the difference in RLS prevalence as a function of age and gender.

**COVARIATES / CONFOUNDERS**

We are interested in whether there are racial differences in the prevalence of RLS and whether these differences are independent of age. For the current analysis, we will not differentiate between idiopathic and secondary RLS and thus we will not control for comorbid diseases when evaluating for racial differences. Other than iron deficiency anemia, pregnancy, and end stage renal disease on dialysis, a clear link to other disorders and RLS has not clearly been established. Because this is a community sample of middle-aged adults, the number of subjects on hemodialysis or women with a concurrent pregnancy is expected to be low and completely negligible.

We are also interested in the impact of RLS on sleep independent of other factors. Below is a list of relevant covariates: age, respiratory disturbance index (RDI) at two different levels of oxyhemoglobin desaturation (3%, 4%), psychiatric medication usage (potential for sleep architecture differences) and self-reported history of angina, PTCA, CABG, stroke, CHF, COPD, and diabetes.

**ANALYTICAL METHODS**

Because the primary objective of the proposal is to describe whether RLS classification is a function of race, we will employ the techniques of multinomial logistic regression. Multinomial logistic models are used to model relationships between a polytomous response variable (i.e., RLS group status) and a set of regressor variables. These polytomous response models can be classified into two distinct types, depending on whether the response variable has an ordered or unordered structure. In an ordered model, the response $Y$ of an individual unit is restricted to one of $m$ ordered values. In an unordered model, the polytomous response variable does not have an
ordered structure. For the current analyses, RLS status can be conceptualized as an ordered or an unordered outcome. Thus, both types of multinomial models will be constructed to determine whether race is cross-sectionally associated with RLS group status. In the construction of these logistic regression models, adjustments for age and gender are possible by inclusion of these variables as covariates in the model. The LOGISTIC and CATMOD procedures in SAS allow for construction of such models and provide estimation (based on maximum likelihood) of parameter estimates (and thus odds ratios) for covariates of interest and the associated standard errors. As with the simple logistic model case, model fit will be assessed by examining index plots of the Pearson residuals and the deviance residuals.

For the purpose of examining sleep related parameters as a function of RLS group designation, appropriate regression techniques will be utilized. For the case of sleep latency, survival techniques will be employed. For modeling sleep stage distributions, the techniques of quantile regression will be used. The choice of quantile regression is based on the previous observations that stage 1 and slow wave sleep in the Sleep Heart Health Study are not normally distributed. Quantile regression models relax the assumptions of linear regression and allow a more flexible depiction of the distribution as a function of covariate data.

To determine whether RLS group is a predictor of hypertension status, logistic regression (binary outcome of hypertension status) will be utilized. Adjustments for age, gender, BMI, race, smoking and other relevant covariates will be included to determine whether RLS status predicts prevalent hypertension at the SHHS II visit.

5. **Type of Study:** Analysis (local); Paper: Secondary.

6. **Type of Publication:** Journal Article

7. **Analysis Responsibility:** Local

8. **Background:**

Restless Legs Syndrome (RLS) is a common sleep disorder; the symptoms produce an intolerable discomfort impacting evening rest, sleep and ultimately on quality of life. Epidemiological studies based on Caucasian populations have demonstrated prevalence rates between 7% and 15%, with higher rates noted in females and with advancing age (2, 4-6). Studies on Asian populations and a Turkish sample have shown lower prevalence rates of 0.6% and 3.2%, respectively (7, 8). In the United States there are no population-based studies examining racial difference in RLS prevalence. A study of hemodialysis patients found African Americans were less likely to complain of restless legs. However, that study was based on a single question in a population known to be difficult to diagnosis with RLS (11, 12). A diagnosis of RLS is based on symptom complaints with no biological marker or physical examination finding specific for the disorder. Variability in reporting of symptoms may lead to inaccurate characterization and prevalence estimates of RLS. Several questionnaires have been used to identify individuals with RLS. One such validated questionnaire was included in association with the second polysomnographic examination of the SHHS (13).

Racial differences in disease prevalence can lead to an understanding of underlying pathology for a disorder. Associated causes and risk factors for RLS include anemia, hemodialysis, and pregnancy (including number of pregnancies), all have been hypothesized to have iron loss or iron dysfunction as their common link. The reason behind this assumption is based on studies of idiopathic RLS patients demonstrating lower CSF ferritin levels and brain iron content (14, 15). Racial differences in iron status report African Americans to have, lower transferrin saturations, higher serum levels of
transferring receptor and lower hemoglobin but higher ferritin levels compared to Caucasians (16, 17). These somewhat paradoxical values reported in African Americans suggest relatively higher rates of erythropoiesis but with the ability to maintain adequate iron stores. Thus, any racial difference in RLS prevalence could help further elicit alterations in iron regulation in relationship to developing RLS.

Because RLS symptoms have a strong circadian and rest component, the primary impact of RLS is on sleep. Laboratory based reports in RLS have been centered on the periodic limb movements or changes with treatment (18). Only two studies compare basic sleep laboratory findings including total sleep time, and wake after sleep, between RLS and normal controls (19, 20). There are even fewer comparisons of sleep parameter abnormalities compared to RLS severity, frequency and age of onset. The impact of RLS on sleep has been felt to be the major contributor to its negative impact on quality of life including a high rate of anxiety and depressive symptoms as well as poor physical health as reported in population surveys (21) (22). Two epidemiological surveys have shown a correlation of hypertension with RLS, but did not relate this to RLS severity or sleep parameters (9, 10). RLS severity in the recent REST study utilized a cut off of moderately or severely distressing symptoms and more than twice per week symptoms as “RLS sufferers”, this group of individuals are the most likely to seek treatment and may be at the greatest risk of developing co morbid disease with RLS (1). Data from the Sleep Heart Health Study survey will allow us to determine the same measurement of RLS severity. When a disorder lacks a clear biological marker and is based on vague seemingly benign complaints it can be easily overlooked, yet a number of studies have now demonstrated what severely affected RLS patients have always known, that this disorder can create significant health concerns. Establishing prevalence rates for different racial and ethnic groups will help to improve diagnosis and identification of RLS.

Reference: