ELSEVIER

Sleep Medicine 8 (2007) 247–251

SLEEP MEDICINE

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Original article

Restless legs syndrome in Indian patients having iron deficiency anemia in a tertiary care hospital

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Received 13 June 2006; received in revised form 2 October 2006; accepted 2 October 2006
Available online 26 March 2007

Abstract

Background and purpose: Prevalence of restless legs syndrome (RLS) in India is unknown. Up to 25% of Caucasian RLS patients also have iron deficiency. The main objective of the study was to find occurrence of RLS in patients with iron deficiency anemia and compare it to non-anemic healthy people.

Patients and methods: This was a cross-sectional study from April 2003 to October 2004 done in in-patient and out-patient services of Medicine department, St. John's Medical College Hospital, Bangalore, India. Sixty-four consecutive adult patients with iron deficiency and 256 age- and sex-matched non-anemic participants were interviewed face-to-face. Hemogram was done in all participants, and free erythrocyte protoporphyrin (FEP) and total iron binding capacity (TIBC) in anemic patients.

Results: RLS symptoms were present in 6.25% of healthy participants and 34.37% of anemic patients ($p < 0.001$). Chronic menorrhagia ($p = 0.001$) and repeated blood donation ($\geqslant 5$ times) ($p = 0.009$) were associated with increased RLS occurrence. RLS was associated with delayed onset of sleep ($p < 0.001$).

Conclusion: RLS, a common occurrence among healthy participants, occurred at a significantly higher rate among iron-deficient anemic patients. Further studies are warranted to better characterize RLS in India.

Keywords: Restless legs syndrome; Iron deficiency anemia; India

1. Introduction

Diagnosis of restless legs syndrome (RLS) has been facilitated by the establishment of specific diagnostic criteria by the National Institutes of Health (NIH) and International RLS Study Group (IRLSSG) [1,2].

In the general Western population, 5–15% suffer from this disorder. To date, studies have shown a high prevalence (up to 25%) of iron deficiency among people with RLS and have postulated the role of iron in brain dopamine metabolism as a putative causative mechanism [3–12]. In these cases, iron supplementation alleviates or even completely cures the condition.

Prevalence of RLS in the Indian population is unknown, which is, in part, because RLS is not recognized as a clinical entity. Few studies on RLS have been done in India so far, none of which have shown its prevalence in the general population [13–15].

Iron deficiency is as highly prevalent as 25–90% even in non-pregnant, non-lactating females in various parts of India [16]. Given the association between iron deficiency and RLS, a large number of these patients are at risk for RLS.

This study was designed to study the occurrence of RLS in patients with iron deficiency and age- and sex-matched non-anemic subjects.

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doi:10.1016/j.sleep.2006.10.004

2. Methods

We did a prospective cross-sectional study from April 2003 to October 2004 on 64 consecutive iron-deficient anemic patients and 256 age- and sex-matched healthy volunteers in St. John's Medical College Hospital (SJMCH), Bangalore, India, after obtaining approval of the Institutional Ethical Review Board of SJMCH.

All respondents were aged 18 years or more. Informed consent was obtained from all respondents prior to inclusion.

Pregnant women and patients with a history of chronic kidney disease were excluded from the study.

2.1. Iron deficiency anemia group

Patients with iron deficiency anemia were defined as those having anemia [(hemoglobin (Hb) <13 gm/dL in males and <12 gm/dL in females) [17]] and iron deficiency [(free erythrocyte protoporphyrin (FEP) > 100 μg/dL, and serum total iron binding capacity (TIBC) > 360 μg/dL) [18]] .

Serum ferritin, the gold standard in diagnosis of iron deficiency, was not used due to limited resources. TIBC taken alone is specific for iron deficiency but lacks sensitivity. On the other hand, FEP is sensitive for iron-deficient erythropoiesis, though not specific [19]. FEP and TIBC were, therefore, coupled to assess iron deficiency, such that high FEP coupled with high TIBC conferred higher sensitivity and specificity for iron deficiency than either taken alone.

Patients were selected from in-patient and out-patient services of the Medicine department. In-patients were selected by review of lab records on a daily basis. Out-patient selection was done through advertisement. Patients diagnosed with iron deficiency anemia on out-patient basis based on hemoglobin, FEP, and TIBC were selected if they voluntarily sought recruitment in the study in response to the advertisement.

Patients who had already undergone blood transfusion or been given parenteral iron prior to interview were not included in the study.

The first consecutive 64 patients fulfilling the above-mentioned criteria were included in the anemia group.

2.2. Healthy group

We defined the healthy group as those not having anemia. Medical co-morbidities apart from pregnancy or kidney disease were allowed. This group comprised volunteers from among staff and attendants of patients in SJMCH and were recruited by direct contact and advertisement. For every anemic patient, four healthy volunteers of the same sex and same five-year age-group-interval were included on a first-come-first-serve basis. This was accomplished by first asking the age of the respondent, and then proceeding with further questioning or tests.

Recruitment for both groups began simultaneously and was completed first in the anemic group so that age- and sex-matching could be achieved in the healthy group.

2.3. Specific tests

Complete hemogram using automated cell counter was done for all participants. Tests done exclusively for anemic patients included FEP (by hematofluorometry), serum iron, and TIBC (by spectrophotometry).

If, in a healthy volunteer, the hemogram indicated anemia, he or she was asked to be tested additionally as in the anemic group. If iron deficiency was established, he or she was then included in the anemic group until the target of 64 anemic patients was met. Once the target of 64 anemic patients was achieved, or if a volunteer did not have iron deficiency or refused further tests, he or she was excluded from the study.

2.4. Interview

All respondents were interviewed face to face using a questionnaire (available in the online version of the article) and examined by the investigator, who was not an RLS specialist. The questions were read to the respondents, and their responses were recorded. When deemed necessary and appropriate, the questions were repeated and elaborated in the vernacular to help ensure proper understanding on the part of the respondent prior to response. RLS was diagnosed if the respondents affirmatively answered all the questions regarding the four essential NIH/IRLSSG criteria for diagnosis of RLS [1]. Those respondents were then questioned regarding allied features of RLS.

During physical examination, emphasis was placed on ruling out secondary causes of RLS and eliciting possible signs of peripheral radiculoneuropathy. No further testing in the form of electroneuromyography or polysomnography was done for any participant.

2.5. Statistical methods

The primary hypothesis was that the presence of iron deficiency would increase an individual's chance of having RLS.

2.5.1. Sample size

The numbers of patients and healthy volunteers (64 and 256 respectively) were chosen based on the assumption that the prevalence of RLS in the general population (as in the West) would be 10% and that there would be an increase in prevalence among iron-deficient anemic patients by 15%, giving a power of 80% for a 95% confidence level.