Study of Iron Metabolism and Restless Legs Syndrome in Blood Donors

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Abstract

Background: Blood donations may be associated with restless legs syndrome (RLS) despite some controversial results. In Spain blood donation is tightly regulated.

Materials and methods: Study of 179 blood donors (56% women, mean age: 43.18 years) divided into sporadic and regular donors. A physical examination (blood pressure, BMI), hemoglobin (discarding subjects with level below 12 gr/dl), blood count and ferritin levels were performed. For the assessment of RLS we personally administered a questionnaire including four questions that probe the necessary features of RLS. We analyzed ferritin and number of positive answers to study the correlation between them.

Results: Twenty-eight (15.4%, 18 women) donors answered positively to at least one question; 9 (4.5%) 2-questions; 10 (5%) 3-questions, 5 (2.5%) 4-questions. Mean ferritin was 48.69 µg/L in women and 131.81 µg/L in men. Women, had a higher risk of at least one RLS positive answer when adjusted for all variables (p=0.053). Regular donors showed a higher percentage of ferritin < 50 µg /L with a significantly lower mean ferritin (p=0.007). Ferritin was<12 µg /L in 4% of donors. We found a significant correlation between ferritin and BMI (p< 0.01). We did not found correlation between ferritin and RLS symptoms.

Conclusions: Regular donors compared with sporadic donors have more frequently ferritin values <50 µg/L. No significant association of ferritin with RLS symptoms was found. Women had lower ferritin and a higher risk of RLS when adjusted for all variables.

INTRODUCTION

Restless Legs Syndrome (RLS) is a neurological condition consisting of sensorimotor disorder primarily involving legs discomfort and motor restlessness [1], worsening of symptoms during evening and night, and partial relief with activity, as well as difficulty in falling asleep and increased number of nocturnal awakenings [2]. The prevalence of RLS is estimated to be of 2-3% in adults [3,4]. Primary RLS cases are often familial, while the secondary RLS cases are sporadic most often caused by iron deficiency, uremia, pregnancy, poly neuropathy and the use of certain medications. In secondary RLS cases are sporadic most often caused by iron deficiency states and low ferritin concentrations [5].

Blood donation has been linked to iron deficiency and anemia. Each donation causes an estimated iron loss of 200-250 mg, which takes six months to be restored; therefore regular blood donation may lead to iron deficiency. A high frequency of iron deficiency among RLS patients was described by Norlander [6]. A serum ferritin concentration below 50 µg /L has been related with the severity of the RLS symptoms [7]. Monitoring blood donors using blood hemoglobin, but not ferritin, may result in a high incidence of iron deficiency without anemia. Thus, has
been hypothesized that donating blood may be a risk factor for developing RLS [8-11] whereas other studies have provided controversial results highlighting the fact that the frequency or number of blood donation up to the maximum of three times a year would not increase the risk of RLS [12-14].

Allen and Early have reviewed the role of central iron deficiency in primary and secondary forms of RLS and documented that both peripheral and Central Nervous System (CNS) iron insufficiency occurs with RLS symptoms [12]. Brain iron insufficiency is supported by independently replicated cerebrospinal fluid and brain imaging studies for patients without iron deficiency anemia [14]. However, a recent study from our FeSPi (Iron Metabolism and RLS Group) showed abnormal iron accumulation in the basal ganglia in a patient with dysmetabolic iron overload syndrome (DIOS), hyperferritinemia and RLS in contrast to previous findings in the literature, suggesting a complex iron metabolism disorder of the CNS [15].

In recent years, several studies have described genetic polymorphisms related to an increase of the risk of RLS, some of them also associated with iron concentrations. However, the impact of these variants on iron levels is unknown in blood donors [16]. The aim of this study which has been performed in two Blood Donation Units from two University Hospitals of the Public Health Service of the Community of Madrid, Spain was to evaluate the status of iron metabolism, and the presence of RLS symptoms in a population of altruistic blood donors. We considered in the analysis: i) ferritin concentration levels, ii) number of positive answers to four RLS-related questions and, iii) the correlation between ferritin values and the number of positive answers related to basic RLS questionnaire.

MATERIAL AND METHODS

This observational study was conducted at the "Gregorio Marañón" University Hospital (Complutense University of Madrid) and "La Paz" University Hospital (Autonomous University of Madrid) (Spain). The study was performed during the period comprises between the 1st January to the 31st December 2014. The study was approved by both local ethic committees and a written patient’s informed consent was obtained in all cases.

In Spain, blood donation is altruistic and tightly regulated, establishing a maximum of 4 donation/year in men and 3 donation/year in women for an age comprises between 18 to 65 years.

Sample characteristics

We recruited for the study 179 blood donors (56% women) mean age: 43.18±11.62 years CI 95% (41.46-44.90). In order to be accepted as potential blood donors all subjects undergo a standard physical examination: anthropometric measurements: weight, height and BMI >18 kg/m² and blood pressure values (systolic >90 mm Hg; 180 mm Hg and diastolic >50 mm Hg and < 100 mm Hg). A capillary hemoglobin test is systematically performed discarding for donation those subjects with hemoglobin < 12 gr/dl (range in men: 13.0-17.5 g/dl and in women: 12.0-16.0 g/dl).

Iron status analysis

A complete blood count analysis was routinely performed. We obtained an extra blood sample (4cc) to determine serum iron (reference range 59-158 µg/dl) and ferritin (reference range 26370 µg/L) concentration levels.

Blood donors were divided in two groups: first time, naïve or sporadic donors and regular blood donors with a mean year’s donation-since first donation (derived from self-report) and mean number donations/year.

Assessment of RLS

For the assessment of RLS we interviewed personally all donors and invited them to complete a questionnaire of four items before leaving the blood donation room. The questionnaire consists of three -RLS related items, which check the mandatory symptoms of RLS as determined by the International Restless Legs Syndrome Study Group (IRLSG) criteria. The fourth question was related to the impact of symptoms on sleep conciliation.

Do you have uncomfortable or unpleasant sensations in the legs such as laying down or sitting?

Does movement, such as walking or stretching, relieve the unpleasant sensations in the legs partially or totally?

Do these unpleasant sensations during rest or inactivity occur only or worsen in the evening or night?

Do the unpleasant sensations allow you to sleep?

Post-donation procedure (1-2 weeks later)

RLS-questionnaire negative and iron status normal: medical discharge.

Iron status abnormal: outcome consultation in the Iron Pathology Unit from Internal Medicine Department.

RLS-questionnaire with more than 3 positive answers: outcome consultation in Neurology Department.

Statistical analysis

The Wilcoxon-Mann-Whitney and Pearson χ² tests were used for the parametric comparison, and the Pearson and Spearman coefficients for quantitative variables. Data are reported as mean±SD. Differences were considered as statistically significant if P< 0.05.

A logistic regression analysis was performed to estimate odd ratios (OR) and 95% confident intervals (CI) in order to demonstrate if regular donation vs first donation was a risk factor to develop RLS and/or ferropenia. For the statistical analysis, we used the IBM SPSS version 21.0 software for Windows.

RESULTS

The subjects were 101 women (56%) and 78 men (44%); 44 (24.58%) of them were first or sporadic donors whereas, 135 (75.42%) were regular blood donors with a mean years donation-since first donation (derived from self-report) - of 10.88±9.44 years, CI 95% (9.29-12.47), and mean number donations/year of 2.06±0.99 years, CI 95% (1.89-2.23).
The mean age of blood donors was: 43.18±11.62 years, CI 95% (41.46-44.90) and the mean BMI 25.86±14.56 Kg/m², CI 95% (25.20-26.52). The hematologic variables showed a mean hemoglobin value of 14.46±1.19 g/dl, serum iron 92.54 ± 31.23 and ferritin 92.21±96.19 level concentrations.

We found a significant positive correlation between ferritin values and BMI (p< 0.01) (Figure 1), and gender differences in ferritin concentration values: women have statistically significant lower ferritin levels [48.69µg/L, CI 95% (40.05-57.33)] compared to men [131.81 µg/L, CI 95% (110.06-153.5)] (p< 0.01) (Figure 2). Ferritin level in first/sporadic donors was 136.47 µg/L, CI 95% (101.89-171.05) vs regular donors 79.72 µg/L, CI 95% (67.60-91.83) and this comparison showed statistically significant difference (p=0.007) (Figure 3).

We analyzed our sample, to see how many donors had ferritin values of 50 µg/L, because this value is considered a "cut-off point" for RLS patients [7]. We found 44% donors with ferritin below 50 µg/L, with a significant predominance of women and regular donors and this comparison was also statistically significant (p< 0.01). We also found 7 donors (5 women and 2 men) with ferritin below 12 µg/L that were regular blood donors (Table 1).

The analysis of four RLS-related questions showed 28 donors (15.4%, 18 women) that answered positively to at least one of the questions (Table 2). In women when compared to men, showed a trend to have at least one RLS symptom when adjusted for all variables (age, ferritin, BMI, sporadic or regular donors) (p=0.053). Regarding the distribution of the responses to the RLS related items, the first question was the one to be more frequently answered positively. No statistically significant correlation was found between ferritin level and number of positive RLS questions (p=0.97) or between ferritin < 50 µg/L and number of RLS responses (p=0.88).

**DISCUSSION**

Data from the REST (RLS Epidemiology, Symptoms, and Treatment) a general population study showed that RLS symptoms were present in approximately 7% of the general population, and 2-3% of this population experienced moderate or severe symptoms at least twice a week [18]. In Spain, the estimated prevalence of RLS is 5.5% in a sub-sample of the REST study. This figure increases up to 11.6% in a population of patients recruited in a primary health care center because of different complaints [19], and up to 14.7% in men blood donors and 24.7% % in women blood donors [8]. The estimated prevalence of RLS patients seeking treatment in Europe is 2.7% to 4.4%, more frequent in older patients and in women with previous pregnancies. In Spain, blood donation is altruistic and regulated (maximum 4 donations/year in men and 3 donations/year in women). All subjects are screened for anemia but not for iron deficiency. Previous studies have determined the iron deficiency indirectly by other procedures like the Red Blood Cell Distribution Width (RDW) [9,10] or Hemoglobin [12,13]. The goal of our study was to detect iron deficiency directly by ferritin concentration levels and its relationship with RLS in...
blood donors. We were intrigued about the existence of such a relationship since in a previous study we reported high serum ferritin levels associated with RLS without iron overload or anemia. In that study 2 out of the 5 reported patients were regular blood donors [20].

Repeated blood donations more than three or four times a year in women and men respectively, increase the risk of iron deficiency [10]. It is well known from studies performed in the general population that there is a gender difference in ferritin levels with lower values in women. In our study we replicated these gender related differences among blood donors (mean ferritin 48 µg/L in women vs 131 µg/L in men), and the difference was statistically significant (p<0.05).

Other RLS studies in blood donors do not distinguish between sporadic and regular donors. In our sample both groups had been separated to analyze possible differences in iron metabolism and RLS between them. When we compare ferritin concentrations values in regular donors vs first-sporadic donors we observed that regular donors had a significantly lower mean ferritin value than naïve or sporadic donors. The hemoglobin value is always higher than 12g/dl as a mandatory requirement to be blood donor in Spain.

We have calculated the number of subjects that would have a ferritin concentration below the cut-off point of 50µg/L to take into consideration the iron deposits deficit in RLS subjects. We found a statically significant ratio of 44% in women regular donors with ferritin below 50µg/L (p<0.05). Seven subjects in the sample had ferritin below 12µg/L (5 women and 2 men) all of them were regular blood donors.

The analysis of the answers to the RLS questionnaire showed a positive answer at least to one of the questions in 28 donors (15.6%) with women predominance. The regression analysis adjusted for all variables showed that women are more likely to answer affirmatively to at least one of the question of the RLS questionnaire (p=0.053). This trend is concordant with the findings of previous studies, where the prevalence of RLS was higher in women blood donors, and even higher in those with iron deficiency measured by RWD [9]. In contrast, we did not found a correlation between ferropenia measured by ferritin concentration values and RLS affirmative responses. Previous studies demonstrated that lower ferritin values correlated significantly with greater RLS severity and decreased sleep efficiency. In our study, all but one patient with severe RLS had ferritin levels < or = 50 µg /L. A study found that patients with lower ferritin levels (< or = 50 µg /L) also showed significantly more periodic leg movements (PLMs) with arousal than did those with higher ferritin levels, but the PLMs/hour ratio was not significantly related to ferritin [5].

These controversial results are probably explained by the differences in the regulation of number donations per year among countries, some of them excluding the anemic subjects; as opposed to blood donation in other countries where blood donation are allowed up to six times a year. Only 2.8% of our donors responded affirmatively to the four RLS related questions, in contrast with the high rates of positive answers in other series [12]. These differences could be probably related to the social-demographic characteristics of the sample and the methodology of the study.

We found a positive correlation between ferritin values and BMI (p< 0.01) in agreement with a recent Aragon Workers’ Health Study in Spain. The authors of this study suggested that ferritin could be a marker of cardiovascular risk, due that its concentration has been related with the metabolic syndrome [21].

Our study has some limitations, as we did not have a control group of non-blood donors to compare our blood donor population prevalence of RLS, and therefore we obtained the prevalence in the general population from published data in our country. Prospective studies in our series including additional iron metabolism parameters are warranted.

CONCLUSION

Regular blood donation, when regulated in similar conditions as in Spain, is associated with a significantly decreased ferritin values <50 µg/L but it does not increase the risk to develop RLS related symptoms. Women blood donors have lower ferritin values and are more likely to have at least one RLS symptom.

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REFERENCES


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