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Sleep Medicine 5 (2004) 115–118

SLEEP
MEDICINE

www.elsevier.com/locate/sleep

Original article

Restless legs syndrome in blood donors

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Received 12 May 2003; received in revised form 18 September 2003; accepted 24 September 2003

Abstract

Background and purpose: Restless legs syndrome (RLS) may be a cause of significant sleep disturbance. In a Swedish survey, the prevalence of RLS has been estimated to be 5.8% among men and 11.4% among women. Blood donation may result in iron deficiency, which is hypothesized to be one substantial cause of RLS.

Patients and methods: Nine hundred and forty-six (618 men, 328 women) consecutive blood donors aged 18–64 years, who attended a blood donation unit in mid-Sweden, answered a questionnaire that included questions about sleep habits. Frequency of blood donation was recorded and intake of iron tablets was assessed. Red blood cell distribution width (RDW) was also recorded. The value of RDW increases in relation to iron deficiency.

Results: RLS affected 14.7% of male and 24.7% of female blood donors. The mean intake of iron among the blood donors after each blood donation was only 781 mg, although the recommended intake is 2000 mg. Among the women, 7.4% presented an RDW of > 14.5%, which strongly indicates iron deficiency. In this group of women, 37.5% were affected by RLS. The female RLS-sufferers were more affected than the female non-RLS subjects by problems initiating sleep ($P = 0.006$), maintaining sleep ($P < 0.0001$) and were also less refreshed upon awakening ($P < 0.001$).

Results: This study showed that RLS was common among female blood donors. Women with RLS were more iron-deficient than those without and were affected by impaired sleep.

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Keywords: Restless legs; Blood donation; Sleep; Sleepiness; Headache; Iron deficiency

1. Introduction

Since 1945, the clinical condition described by Ekbom [1], restless legs syndrome (RLS) has been recognized as an important cause of sleep disturbance. In a recent survey in Dalarna County, Sweden, the prevalence of RLS was estimated to be 5.8% among men and 11.4% among women [2,3].

Iron deficiency is suggested to be a substantial cause of RLS [4–7].

Regular blood donation may constitute a significant cause of iron deficiency, especially in female donors [8]. In Sweden, the recommended iron substitute after each blood donation is 2000 mg, based on the fact that a 200–250 mg iron loss occurs after donation and that the gastrointestinal uptake of iron taken orally is 10% [9]. Ekbom was the first to report two cases of blood donors with concomitant RLS

[10]. Silber and Richardson, as well as Kryger et al. recently reported that repeated blood donation may be associated with RLS [11,12].

The present study compares blood donors who suffered from RLS and those who did not. The study was approved by the Ethics Committee of the Medical Faculty, Uppsala University.

2. Material and methods

Subjects were drawn from 961 consecutive blood donors, aged 18–64 years, who attended the blood donation unit of Avesta Hospital in Avesta, Dalarna county, Sweden, during a 10-month period in 2001. Nine hundred and forty-six (618 men, 328 women) blood donors (98.3%) agreed to enter the study. Mean age of the males was 43.3 years and of the females 41.2 years. No first time blood donors were included in the study.

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To identify those affected by RLS, we translated the four symptom questions determined in 1995 by the International Restless Legs Syndrome Study Group (IRLSSG) as minimal diagnostic criteria for RLS [13]: (a) desire to move the extremities, often associated with paresthesias/dysesthesias, (b) motor restlessness, (c) worsening of symptoms while at rest, with at least temporary relief by activity, and (d) worsening of symptoms during the evening or at night. A positive response to all four questions indicates RLS. The criteria were translated from English to Swedish by five Swedish sleep researchers and an authorized translator with English as their native language [14].

The subjects also responded to a questionnaire about symptoms of insomnia and complaints of headache experienced during the previous 6 months. A five-point scale was used to assess the frequency of symptoms related to initiating and maintaining sleep, <6 h of sleep, frequency of morning and daytime headache, and not being refreshed on awakening. The alternatives on the five-point scale were: never, sometimes, sometimes per month, sometimes per week, and daily.

Subjects filled out the Epworth Sleepiness Scale (ESS), a simple instrument that has been validated and used worldwide for evaluating excessive daytime sleepiness [15].

Frequency of blood donation, as well as intake of any type of iron tablet during the previous year, was recorded by the blood donation unit and assessed by the blood donor him/herself.

Red blood cell distribution width (RDW), estimation in percent of the average distribution of red blood cell diameter, was recorded along with hemoglobin (Hb) count. The analysis was done by Beckman-Coulter MAXM blood analyzing system. The value of RDW increases in relation to iron deficiency, in one report estimated by using ferritin values as a reference [16].

3. Statistical analysis

Prior to statistical analyses, we dichotomized category responses to the questions concerning problems with initiating sleep, maintaining sleep, <6 h of sleep, frequency of morning and daytime headache, and not feeling refreshed on awakening. The responses 'never, sometimes, and sometimes per month' were classified as 'no' and responses 'sometimes per week and daily' were classified as 'yes'.

Statistical analyses were performed by Student's *t*-test and Fisher's exact test.

A *P*-value <0.05 was considered as statistically significant. Statistical analyses were performed with a software program (SPSS/PC + 5.01, SPSS Inc., Chicago, IL).

4. Results

According to the questionnaire response, 91 (14.7%) of the male blood donors and 81 (24.7%) of the female blood donors were affected by RLS. The association between age, blood donation frequency, hemoglobin, RDW, and the intake of iron by RLS-positive or RLS-negative participants is presented by gender in Table 1.

Total mean intake of iron during the previous 12 months was 1641 mg [1676 mg among non-RLS subjects vs. 1481 among those affected by RLS, (NS)]. The women consumed more iron than the men during the study period (1927 vs. 1494 mg, *P* < 0.01).

Among the men, 17/618 (2.8%) had an RDW of >14.5%; 2/17 men in this group (11.8%) were affected by RLS. The corresponding figures among the women were 24/324 (7.4%) with an RDW of >14.5%; 9/24 (37.5%) were affected by RLS. The mean intake of iron among these women was 1165 mg. Mean blood donation frequency in

Table 1

Values of different characteristics in blood donating female RLS-sufferers (*n* = 81) and those without RLS (*n* = 247) and male RLS-sufferers (*n* = 91) and those without RLS (*n* = 527)

		Women			Men		
		Mean	SD	<i>P</i> -value	Mean	SD	<i>P</i> -value
Age/years	Non-RLS	40.2	11.2	0.007	43.3	11.2	NS
	RLS	44.1	10.7		43.6	9.2	
Blood donation frequency past year	Non-RLS	1.7	0.7	NS	2.3	0.9	NS
	RLS	1.8	0.7		2.4	1.0	
Hemoglobin (g/l)	Non-RLS	131.7	8.2	NS	146.4	7.4	NS
	RLS	132.2	7.8		147.9	10.9	
RDW (%)	Non-RLS	13.06	0.83	0.031	12.95	0.69	NS
	RLS	13.30	1.02		12.85	0.63	
Intake of iron past year (mg)	Non-RLS	1967	1613	NS	1542	1825	NS
	RLS	1795	1528		1236	1411	

SD, Standard deviation.

Table 2

Assessments of variables on sleep and headache from blood donating female RLS-sufferers ($n = 81$) and those without RLS ($n = 247$) and male RLS-sufferers ($n = 91$) and those without RLS ($n = 527$)

Variable	Women			Men		
	RLS N (%)	Non-RLS N (%)	<i>P</i> -value	RLS N (%)	Non-RLS N (%)	<i>P</i> -value
Problems initiating sleep	20 (24.7)	28 (11.3)	0.006	15 (16.5)	42 (8.0)	0.02
Problems maintaining sleep	19 (23.5)	18 (7.3)	<0.0001	11 (12.1)	38 (7.2)	NS
Not refreshed at awakening	31 (38.3)	46 (18.6)	<0.0001	25 (27.5)	108 (20.5)	NS
Less than 6 h of sleep each night	19 (23.5)	36 (14.6)	NS	29 (31.9)	112 (21.3)	0.03
Daytime headache	8 (9.9)	19 (7.7)	NS	5 (5.5)	16 (3.0)	NS
Morning headache	5 (6.2)	7 (2.8)	NS	2 (2.2)	13 (2.5)	NS

this group was 1.9 donations per year. Mean age in this group of women was 47.7 years.

The mean values of the scores on the ESS in both the male and female RLS-sufferers was higher than in those not affected by RLS (9.7 vs. 7.7, $P < 0.001$ and 8.8 vs. 7.2, $P = 0.003$).

The female RLS-sufferers were more affected than the female non-RLS-subjects by problems initiating sleep ($P = 0.006$), maintaining sleep ($P < 0.0001$) and they were less refreshed upon awakening ($P < 0.001$) (Table 2). Problems initiating sleep ($P = 0.02$) and night sleep < 6 h were more often reported among the male RLS-sufferers than the male non-RLS-subjects ($P = 0.03$) (Table 2).

5. Discussion

In this study we observed the highest frequency of RLS among blood donating women. When compared with studies among the general population [2,3], we acknowledge that our findings overestimate the frequency of RLS. We focused on RLS issues in the written and verbal material given to the participating subjects. We did not ascertain whether the subjects suffered from RLS prior to becoming blood donors or the duration in years of blood donation, and the absence of a control group and clinical evaluations may have further contributed to the uncertainty of our figures. On the other hand, the high response rate makes our outcome reliable. Since the subjects in recent epidemiological studies were chosen from the same population as those in the present study [2,3], a future controlled study with a comparison population, answering the same questionnaire, would be of great value.

Although clinical evaluation of our subjects would have been informative, we do not believe it plausible that other confounding factors, such as disease or drug intake, were the cause of RLS in this population. Blood donors are deemed to be in good health, drug-free, honest about their health status and unmotivated by financial compensation (about US\$ 4 for each donation). A cut off point of $> 14.5\%$ for RDW has 59% specificity for iron deficiency [16]. RDW

values $> 14.5\%$ should represent iron deficiency in donors otherwise in good health.

Estimations of ferritin in serum would have been of value, but would have cost about US\$ 20 000 for the nearly 1000 subjects involved. A single blood sample for RDW is seldom used in clinical practice. We chose the RDW value $> 14.5\%$, with a 94% sensitivity for iron deficiency [16], as a tool to indirectly detect iron deficiency. There was no extra charge for the Hb and RDW tests, as these samples were analyzed as part of the blood donating process.

It is important to make clear that the data presented in this study do not indicate that blood donation itself is a cause of RLS. However, the mean donation frequency during the previous year was 2.1, and mean intake of iron after each donation $1641 \text{ mg}/2.1 = 781 \text{ mg}$, a much lower dose than that recommended. Net losses of iron over several years may lead to a substantial negative impact on iron metabolism. A record of the duration in years of blood donation might have been useful. However, the yearly intake of iron supplements is considered insufficient to compensate for iron loss from blood donation [9], and therefore, such assessment would not have shed light on the question of long-term iron metabolism.

Earlier data indicating a relationship between iron deficiency and RLS referred mainly to women; 13/18 with RLS in the study by O'keeffe et al. [4], and 18/27 with RLS in the study by Sun et al. [5]. In our study, a relationship between iron deficiency and RLS was observed only among the female blood donors; more of the RLS than the non-RLS subjects in this group showed signs of impairment of red blood cell production. The women with RLS were older than the women without RLS, and our findings may reflect the fact that RLS progresses with age [2] and that women near menopause, have had time to develop more iron deficiency due to menstrual iron losses than younger women.

Although the intake of iron was higher among women than among men, the women showed a higher frequency of RLS than the men, perhaps due to the gender difference in RLS-prevalence [17], or to a gender-based susceptibility for iron deficiency among women. RLS might be an individual- and gender-based disorder of blood-brain barrier iron

transport, as recently reported by Earley et al. [18]. Those who suffer from RLS might need greater iron intake than non-RLS subjects in order to attain higher ferritin levels [7].

In general, complaints of insomnia are more common among women, and the higher figure of RLS among women than men may be a contributing factor [3]. The finding in this survey, that women with RLS have more symptoms of insomnia than women without RLS, gives further support to the argument that RLS may cause sleep impairment even in those who do not seek medical advice for restless legs [2,3].

In conclusion, this study shows that the occurrence of RLS is high among blood donating women, and that these subjects are affected by sleep complaints as well as sleepiness. It is hypothesized that iron deficiency may be one pathophysiological factor contributing to RLS. Further studies in this area are warranted.

Acknowledgements

We are grateful to Jan Ifwer for support with statistical calculations and the staff of the Blood Donation Unit, Avesta Hospital, for assistance in performing the study.

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