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# Prévalence du syndrome des jambes sans repos chez les donneuses de sang, une semaine après un don

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# Prévalence du syndrome des jambes sans repos chez les donneuses de sang, une semaine après un don

THESE

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**Prévalence du syndrome des jambes sans repos chez les donneuses de sang, une semaine après un don de sang – Résumé de l'étude**

Le syndrome des jambes sans repos (SJSR) est une pathologie fréquente dont la prévalence dans la population générale est de 5-15%. Le SJSR se caractérise par un besoin impérieux de bouger les membres inférieurs qui apparaît le plus souvent au repos, le soir et la nuit. Les symptômes sont typiquement atténués par la mobilisation des jambes. Plusieurs études ont montré que le SJSR a d'importantes répercussions sur le quotidien des patients atteints avec une diminution de leur qualité de vie, des troubles du sommeil et une altération des fonctions cognitives.

Un lien entre la carence martiale et le SJSR est supposé depuis plusieurs dizaines d'années. Il a été montré que les symptômes sont aggravés en cas de déficit en fer sans qu'une corrélation directe ait pu être établie, le taux de ferritine étant souvent normal chez les patients avec un SJRS. Des études plus récentes ont permis de montrer qu'il existe une carence en fer au niveau du système nerveux central des patients avec un SJSR notamment au niveau du liquide céphalo-rachidien et de la substance noire. Il existe une probable dysfonction du système dopaminergique qui explique la symptomatologie des patients et la réponse souvent favorable aux agonistes dopaminergiques. Par ailleurs, des études ont récemment montré qu'il existe des polymorphismes de plusieurs gènes chez les patients avec un SJSR faisant supposer une probable prédisposition génétique.

Les femmes donnant leur sang, population préalablement en bonne santé, sont plus à risque de présenter une carence en fer qui pourrait être associée à une augmentation du risque de développer un SJSR. Les études à ce sujet ont montré des résultats contradictoires. Une étude suédoise parue en 2004 montrait une prévalence du SJSR chez les donneuses de sang de presque 25% alors qu'une étude américaine de 2010 décrivait une prévalence de 9% comparable à la population générale. Il est donc d'intérêt de savoir si l'on fait prendre un risque aux donneuses de sang de développer une affection invalidante telle que le SJSR.

Le but de ce travail de thèse en médecine était donc de déterminer la prévalence du SJSR chez les donneuses de sang. Une semaine après un don de sang, on demandait aux sujettes de répondre aux quatre questions diagnostics définies par le *1995 International RLS study group* (groupe d'expert sur le SJSR). Le diagnostic de SJSR était retenu en cas de réponse positive aux quatre questions. Dans les objectifs secondaires, nous avons également évalué l'hyperménorrhée, la fatigue, la capacité aérobique, la fréquence des dons et la qualité de vie et les paramètres hématologiques.

Notre étude s'est déroulée de 2008 à 2010 et notre collectif comprenait 291 donneuses de sang de 18 à 49 ans. Nos résultats ont montré une prévalence du SJSR de 6.9% chez les donneuses de sang. La prévalence de l'hyperménorrhée était augmentée chez les donneuses avec un SJSR et elles étaient également significativement plus fatiguées. Nous n'avons pas montré d'association entre le SJSR et la capacité aérobique, la fréquence des dons et la qualité de vie. Comme montré dans plusieurs études, nous avons confirmé l'absence de lien entre le SJSR et le taux d'hémoglobine et la ferritine.

En conclusion, notre étude a permis de montrer une prévalence du SJSR chez les donneuses de sang comparable à celle de la population générale. Elle n'est donc pas aussi importante que décrite dans certaines études ce qui devrait rassurer les donneuses. Une association entre le SJSR et l'hyperménorrhée et la fatigue devrait nous encourager à les dépister chez les donneuses de sang.

A noter finalement que parallèlement à ce volet de notre étude présenté dans cette thèse, nous avons également cherché à évaluer l'efficacité d'un traitement substitutif de fer chez les donneuses de sang présentant une carence en fer sans anémie, sujet de deux autres articles.

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# Prevalence of restless legs syndrome in female blood donors 1 week after blood donation

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Vox Sanguinis

**Background and Objective** Restless legs syndrome (RLS) is a frequent condition with a prevalence of 5–15% in the general population. Clinical and genetic observations have shown that iron deficiency, highly prevalent among blood donors, can be related to RLS. The objective of this study was to assess the prevalence of RLS in female blood donors 1 week after blood donation.

**Methods** One week after blood donation, 291 female blood donors, aged <50 years, self-responded to all four RLS questions defined by the 1995 International RLS study group. Blood donation rate, fatigue, aerobic capacity, menstruation, mood disorder and quality of life were also assessed along with haemoglobin and ferritin blood concentrations.

**Results** Prevalence of RLS in female blood donors 1 week after blood donation was 6·9% (CI 95% 4·2–10·4%). Female blood donors with RLS had a higher prevalence of hyper-menorrhaea ($P = 0{\cdot}033$) and were significantly more tired ($P = 0{\cdot}001$). We observed no associations between RLS and number of previous donations ($P = 0{\cdot}409$), aerobic capacity ($P = 0{\cdot}476$), mood disorder ($P = 0{\cdot}169$), quality of life ($P = 0{\cdot}356$), haemoglobin ($P = 0{\cdot}087$), and serum ferritin level ($P = 0{\cdot}446$).

**Conclusion** Restless legs syndrome prevalence in female blood donors is not as important as described in some other studies, which could reassure blood donors. The prevalence of hypermenorrhaea and fatigue is higher in RLS blood donors. Therefore, screening for fatigue and hypermenorrhaea could be considered as these symptoms are associated with RLS in female blood donors.

**Key words:** blood donation, fatigue, hypermenorrhaea, iron deficiency, restless legs syndrome, sleep disorder.

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## Introduction

Restless legs syndrome (RLS) is characterized by an urge to move the legs, often associated with paresthesias. Symptoms usually appear while the patient is at rest, lying down or sitting. The symptoms get worse in the evening and at night, and are typically relieved by voluntarily moving the legs.

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Restless legs syndrome prevalence in the general population is 5–15% [1–5]. The REST study, a large multicentric prevalence study including five European countries and the USA, showed a prevalence of RLS of any frequency of 7·2% in a study population of 16 202 adults [2]. There was no significant difference between countries. This study also showed that the prevalence was twice as high among women, which was confirmed in other studies [2, 5–7]. Restless legs syndrome has important implications in everyday life. Sleeping impairment, diminished cognitive functions and reduced quality of life have been described [2, 6].

A link between iron deficiency and RLS was suggested in the sixties by Ekbom [8], a pioneer in the study of this disease. Symptom severity has been correlated with serum ferritin levels <50 μg/l [9]. A study in which the ferritin level was measured in cerebral spinal fluid (CSF) showed lower concentrations in RLS patients [10]. Another study estimating cerebral iron load with magnetic resonance imaging (MRI) demonstrated decreased iron in the substantia nigra [11]. Furthermore, Stefansson found a genetic link between iron deficiency and RLS [12], which was confirmed in blood donors by Sorenson [13].

Because of iron loss related to blood donation [14], RLS could be more prevalent in blood donors. A Swedish study [15] showed a markedly increased prevalence of RLS among female blood donors (24·7%) and, according to a clinical trial [16] carried out by the same group of researchers, administration of intravenous iron relieved these symptoms. However, the association with blood donation was not confirmed in an American study [17], which showed a similar prevalence of RLS in donors compared with the general population (9%). A recent study also showed a prevalence of RLS of 9% in donors [18].

These contradictory results are important to clarify. Potential blood donors may stop giving blood if they are exposed to the risk of developing a disabling condition such as RLS [1, 6, 19, 20]. We studied childbearing-aged female blood donors who are particularly at risk of iron deficiency. We assessed the prevalence of RLS in Switzerland a week after blood donation, when both haemoglobin and ferritin are supposed to be at their lowest levels, and a possible association with menstrual bleeding, number of donations in the previous year and biological parameters (ferritin, haemoglobin). We also assessed the association of RLS with fatigue, aerobic capacity, mood and quality of life.

## Methods

### Study design

This was a nested prevalence study within a randomized controlled trial [21]. The purpose of the latter study was to evaluate the clinical effect of an iron treatment among non-anaemic but iron-deficient female blood donors.

### Participants

All consecutive women attending the Lausanne Blood Transfusion Service of the Swiss Red Cross, aged 18–50 years, and who met eligibility criteria for blood donation according to Swiss national regulations, were invited to participate in a clinical trial investigating iron deficiency in female blood donors. Exclusion criteria were psychiatric conditions or diseases that rendered the participant unable to give consent; thyroid, hepatic, rheumatic, kidney, cardiopulmonary, or intestinal disease; acute or chronic inflammation; diabetes; hemochromatosis; pregnancy; medical treatment that could alter iron absorption and any iron supplementation [22].

Subjects were recruited at Lausanne's Blood Transfusion Service of the Swiss Red Cross during their usual visit. In Switzerland, blood is donated on a voluntary basis without any financial benefit to the donor. Subjects were women, aged 18–50 years, eligible to donate blood according to the eligibility criteria of the Swiss Red Cross. One week after their blood donation, volunteers were then followed-up by two nurse practitioners at the Department of Ambulatory Care and Community Medicine of Lausanne University Hospital.

Criteria for clinically-relevant RLS were defined by positive responses to all four questions defined by the 1995 International RLS study group [23] (Table 1).

Possible RLS was defined as those who responded positively to the first question, but not to all the other questions, as it has been suggested that milder or subclinical forms of RLS might exist [7]. Controls were those who responded negatively to the first question.

On the same day of the blood donation, we collected information on age, number of previous blood donations during the past year, past medical history, medications taken, biological markers (haemoglobin and ferritin), and Fatigue Severity Scale (FSS) [24]. One week after donation, patients self-responded to the four RLS questions defined by the 1995 International RLS Study Group [23] and completed Janssen's *Pictorial Bleeding Assessment Chart* [25] to detect hypermenorrhea (cut-off point set at 100 points [26]), the Patient Health Questionnaire (PHQ-9)

**Table 1** Restless legs syndrome (RLS) four questions defined by the 1995 International RLS study group [23]

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (Sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs)
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night (When symptoms are very severe, the worsening at night may not be noticeable but must have been previously present)

[27] to detect mood disorders, and the short form (SF-12) [28] to measure quality of life (defined as the sum of the physical and mental health scores). Aerobic capacity was measured with a step test (Chester Step Test) [29] as an objective measure of muscular fatigue. Haemoglobin, ferritin, FSS and a fatigue Visual Analogical Scale were also collected at that time-point. C-reactive protein (CRP) level was added to exclude increased ferritin owing to inflammation.

### Statistical methods

We wished the study detect a fourfold odd ratio of RLS for those with low ferritin level compared with those with higher ferritin level. From previous studies, the prevalence of blood donors with low ferritin (<15 μg/l) was assumed to be approximatively 20%. We therefore powered the study to detect a difference from 20% of RLS in the low ferritin group compared with 5% of RLS in other donors with a ratio of 1/5 in the number of donors in each group. With a significance level set to 0·05 and a power of 0·80, this required including 45 donors with low ferritin and 224 donors with high ferritin. Assuming 10% of missing data, 296 participants were to be included. The study was nested within a clinical trial. Full data were therefore obtained from 291 participants.

The prevalence of RLS was measured with 95% confidence intervals (CI). Subjects were classified into one of three groups; no RLS, possible RLS, and definite RLS. Pre- and postdonation averages of measures were compared between groups using one-way analysis of variance (ANOVA). For nominal characteristics, we used Fisher's exact test. Results were confirmed using a non-parametric test (Mann–Whitney). Logistic regression was used to measure the odds of having RLS at 1 week. For multivariate analysis, determinants that showed a significance level of $P < 0{\cdot}2$ were retained. Missing data were not replaced. The study obtained ethical approval from the official biomedical state ethics committee under the reference 131/08.

## Results

A total of 736 female blood donors were invited to participate and 313 gave their informed consent prior to donation between December 2008 and September 2010. Twenty-two participants did not answer the RLS questionnaire 1 week after donation; thus, 291 women were included in the study. The main reason (79%) for non-participation was lack of availability for personal reasons.

The mean age of the participants was 31·1 [SD = 9·2; range (18–51·5)] years, and the average frequency of blood donation during the past year was 0·9 [SD = 0·8; range (0–3)] times. Further description of the blood donors is provided in Table 2.

One week after blood donation, 20 of the 291 donors responded positively to all four questions defined by the 1995 International RLS Study Group. The observed prevalence of clinically relevant RLS was, therefore, 6·9%. The prevalence in the possible RLS group was of 20·6% (60 of the 291 donors). One week after blood donation, prevalence of ferritin below 30 μg/l was 85·6% (249), below 25 μg/l was 77·3% (225), below 15 μg/l was 51·9% (151).

Donors with RLS reported higher levels of fatigue ($P = 0{\cdot}001$) and blood loss due to menstruation ($P = 0{\cdot}033$) compared with those without RLS. We did not observe any significant differences between groups for number of previous donations, levels of ferritin or haemoglobin, aerobic capacity, or quality of life (Table 2). Hypermenorrhaea, FSS scores, depression measured with the PHQ-9, and the SF-12 mental health scores were potentially associated with RLS (Table 2). Multivariable analysis showed that fatigue before donation, hypermenorrhaea and quality of life after donation were independently associated with RLS (Table 3).

## Discussion

In our study, the prevalence of clinically-relevant RLS in female blood donors 1 week following blood donation was 6·9%, which is similar to the prevalence observed in the general population [1–5]. Female blood donors with RLS had a higher prevalence of hypermenorrhaea and reported significantly more fatigue. Nevertheless, there was no association with the number of previous blood donations and objectively measured physical fatigue. As in several other studies [30], we found no correlation between systemic iron status and RLS.

The strength of this study is that we not only assessed RLS prevalence, but also many additional parameters. We assessed menstrual bleeding and physical fatigue. We compared haemoglobin, ferritin and fatigue before and after blood donation. Clinical signs were assessed 1 week after blood donation when haemoglobin and ferritin values are consistently lower after blood donation.

As limitations, we were unable to compare RLS prevalence before and after donation because we did not plan to measure it prior to blood donation. Given the small number of donors involved and the low frequency of RLS, an effect of low iron status could be missed since the study is underpowered. Because we studied a healthy population, it was not ethically acceptable to assess CSF iron stock in our study population although this is of interest since it is described as being decreased in patients with RLS [10, 11, 31]. Because our study was transversal, we cannot know if the fatigue was due to RLS or the

**Table 2** Population characteristics

| | No RLS (control) *n* = 231 | Possible RLS *n* = 40 | Clinical relevant RLS *n* = 20 | *P*-value[a] |
|---|---|---|---|---|
| Age in years; average (range) | 32·2 (18–49) | 32·3 (18–51) | 33·2 (18–50) | 0·912 |
| Blood loss | | | | |
| Number of donations during previous 12 months; average (SD) | 0·9 (0·8) | 0·7 (0·8) | 0·9 (0·9) | 0·409 |
| Pictorial bleeding assessment chart, >100; *n* (%) | 69 (29%) | 18 (45%) | 10 (50%) | 0·033 |
| Haematological | | | | |
| Haemoglobin in g/l | | | | |
| Before donation (same day); average (SD) | 133·6 (7·4) | 135·7 (8·3) | 135·2 (9·6) | 0·233 |
| 7 days after donation; average (SD) | 120·6 (7·4) | 123·1 (9·8) | 123·2 (7·8) | 0·087 |
| Ferritin µg/l | | | | |
| Before donation (same day); average (SD) | 37·0 (24·2) | 39·4 (31·1) | 36·7 (33·7) | 0·862 |
| 7 days after donation; average (SD) | 17·6 (14·6) | 18·6 (17·5) | 22·1 (22·5) | 0·446 |
| Fatigue | | | | |
| Chester step test, 7 days after donation ($VO_2$ max); average (SD) | 36·6 (6·3) | 36·2 (5·8) | 34·9 (4·8) | 0·476 |
| Fatigue severity scale (range 1–9) | | | | |
| Before donation (same day); average (SD) | 2·6 (1·1) | 3·2 (1·1) | 3·3 (1·5) | 0·001 |
| 7 days after donation; average (SD) | 3·2 (1·5) | 4·1 (1·4) | 4·1 (1·7) | 0·001 |
| Health status (7 days after donation) | | | | |
| Depression PHQ-9; *n* (%) | 5 (2·2%) | 9 (22·5%) | 1 (5%) | <0·001 |
| SF-12 physical health (SD) | 53·4 (4·3) | 54·1 (4·6) | 52·2 (6·1) | 0·356 |
| SF-12 mental health (SD) | 41·0 (5·4) | 39·2 (6·9) | 39·7 (5·5) | 0·169 |

ANOVA, analysis of variance; RLS, restless legs syndrome; SD, standard deviation; PHQ, Patient Health Questionnaire; SF, Short Form.
[a]ANOVA or Fishers exact test.

**Table 3** Predictors of restless legs syndrome, 7 days after blood donation

| | Odds ratio of having RLS | |
|---|---|---|
| | Crude OR | Adjusted[a] OR (95% CI; *P*-Value) |
| Pictorial bleeding assessment chart >100 | 2·07 | 2·04 (1·08–3·90; *P* = 0·029) |
| Haemoglobin after donation <120 g/l | 0·80 | 0·80 (0·41–1·54; *P* = 0·501) |
| Fatigue Severity Scale | | |
| 0–2·9 points (Reference) | 1 | 1 |
| 3–3·9 points | 1·58 | 1·56 (1·11–2·20; *P* = 0·011) |
| 4–4·9 points (SD) | 2·81 | 2·43 |
| 5–5·9 points | 5·63 | 3·80 |
| Depression PHQ-9 | 9·04 | –[b] |
| SF-12 mental health | | |
| ≥35 points (reference) | 1 | 1 |
| 30–34 points | 2·04 | 1·48 (0·86–2·53; *P* = 0·154) |
| 20–29 points | 3·40 | 2·19 |

OR, odds ratio; CI, confidence interval; SF, Short Form; PHQ, Patient Health Questionnaire.
[a]Full data was available for 272 participants.
[b]Patient Health Questionnaire-9 was dropped due to co-linearity with SF-12 mental health.

opposite. The severity and duration of RLS were not studied. External validity only applied to female blood donors. There was no non-blood donor control group.

Our results were significantly different from those of the Swedish study that showed a RLS prevalence of 24·7% in female donors [15]. As pointed out by the authors, the results were probably overestimated by methodological problems, although they used the same criteria as in our study. In a US study [17], the prevalence of RLS in blood donors from both sexes was 9%, with a distinction between possible RLS (5%) and definite RLS (4%). In our study, we also defined a possible RLS group that included the population who described an 'urge to move the legs' (first criterion) and not all three of the others. The prevalence in this group was much higher (20·6%) compared with the US study, but they did not use the same tool to define the RLS and possible RLS groups [32, 33]. It remains that this population could have a milder or subclinical form of RLS, and further longitudinal studies could be of interest to determine if some of them develop RLS later on. Finally, contrary to the studies cited above, we measured RLS prevalence a week after donation at the expected nadir of serum ferritin. We do not know if that had an influence on the measured prevalence and whether it would have been different if we

looked for RLS a few weeks after blood donation. Other studies are also needed.

The REST study [2], a general population study, showed that the prevalence of RLS increases with age up to age 80 years then declines. RLS prevalence in younger patients was lower than in our study. Thus, it remains possible that the prevalence of RLS may be slightly higher in blood donors compared with a general population of the same age.

The RLS and possible RLS groups also reported significantly more tiredness after blood donation than other blood donors. A recent study found an association between fatigue severity scores and heavy menstrual bleeding in young women [34]. Therefore, it is important to think of RLS among tired blood donors because RLS is easy to diagnose with minimal cost, whereas investigations of fatigue can quickly generate significant costs.

Our study did not show any correlation between RLS and haemoglobin and ferritin levels or the number of previous blood donations, which was already demonstrated in previous studies [7, 15, 17, 18, 30, 35]. Recent studies suggested that intravenous iron treatment improves the symptoms of RLS in some patients [16, 30, 35, 36–38]. The correlation between hypermenorrhea and RLS found in our study suggests that prolonged iron loss is more predictive of RLS than systemic iron status and number of previous donations. One explanation could be that unlike menstruation, iron loss related to blood donation probably does not happen on regular intervals throughout a premenopausal woman's life. Moreover, female blood donors, who can donate twice a year, have often already shown a good tolerance to successive blood donation. Furthermore, systemic iron status does not reflect intracerebral iron stores, which is reduced in the CNS of RLS patients [10, 11, 31, 39]. The main hypothesis is that iron deficiency in some brain regions (midbrain) would result in a malfunction of the dopaminergic system leading to symptoms of RLS [5, 40].

Genetic predisposition could also play a role as several gene polymorphisms predictive of RLS have been identified [12, 41–44]. In the future, progress in this area could even show that subjects genetically predisposed to RLS are simply more sensitive than normal subjects to iron deficiency.

In conclusion, we found that the RLS prevalence in female blood donors is not as important as described in some other studies. Therefore, our findings should reassure blood donors. However, screening for fatigue and hypermenorrhea should be considered as these symptoms are associated with RLS in female blood donors.

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