



Original Article

Prevalence of restless legs syndrome and associated factors in an otherwise healthy population: results from the Danish Blood Donor Study



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ABSTRACT

Objective: Restless legs syndrome (RLS) is a neurological sensorimotor disorder characterized by uncomfortable sensations in the legs. RLS often occurs as a comorbid condition. Besides an increased risk of iron deficiency, blood donors are considered to be generally healthy. Blood donors are therefore an ideal population for studying factors associated with RLS occurrence, herein the role of iron. It is suggested that RLS is linked to sex, age, low socioeconomic status, unhealthy lifestyle, and iron deficiency. The objective of this study is therefore to estimate the RLS prevalence and identify associated biological, sociodemographic, economic, and lifestyle factors in a population of blood donors.

Methods: A total of 13,448 blood donors enrolled in the Danish Blood Donor Study from May 2015 to May 2016. RLS cases were identified using the validated Cambridge–Hopkins RLS-questionnaire. Logistic regression models were applied to assess the relationship between RLS and data on socially related factors collected using questionnaires and population registers.

Results: In this study, 7.2% women and 4.5% men were classified with RLS. RLS was associated with: female sex, high age, smoking, frequent alcohol consumption, and low education. RLS-related symptoms were associated with obesity, parity and donation intensity three years prior to inclusion among women. RLS was not related to: reduced plasma ferritin, employment status, and income.

Conclusions: RLS is a frequent disorder in otherwise healthy individuals. The associations discovered in this study can be utilized in preventing or reducing RLS symptoms.

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Restless legs syndrome (RLS), also referred to as Willis–Ekbohm disease, is a common neurological sensorimotor disorder, which is characterized by uncomfortable sensations in the extremities – predominantly in the legs. RLS-sufferers experience an urge to move their legs, which is often associated with paresthesia [1]. The

symptoms become worse during rest and increase in intensity in the evening and at night. Many RLS-sufferers also experience involuntary jerking of the legs, which can cause sleep problems that increase the risk of subsequent morbidity [2]. RLS affects between 5 and 11.5% of the general population in European countries and in the USA, with the prevalence increasing with age and a higher risk among women [2,3]. Despite the high prevalence, the disorder seems underdiagnosed as many affected individuals may not seek help and health professionals have limited focus on the disorder [4,5]. RLS can occur as an idiopathic, often hereditary disorder, which is referred to as primary RLS. It can also occur as secondary RLS, which is when the disorder associates with other medical conditions, such as iron deficiency, end-stage renal disease, or pregnancy [2] – conditions that all affect iron metabolism. This gives us reason to believe that RLS may be common among blood donors, because donors are at increased risk of iron depletion caused by donations. It has previously been shown that the frequency of blood donations over a three-year period is a strong predictor of iron deficiency among blood donors [6]. Women have an increased risk of developing RLS and the risk increases with age, which also seems true for individuals of low socioeconomic status [7]. Nulliparous women, however, have been found to have the same risk as same-age men [8] and it is suggested that the risk increases with number of pregnancies [9]. Furthermore, a dose–response relationship between an increased number of healthy lifestyle factors is present (normal body mass index (BMI), non-smoking, regular exercise, and low alcohol consumption) and lower risk of RLS is reported [10].

Individuals eligible for donation are generally healthy. Thus, this group of people is at low risk of developing RLS due to other medical conditions and is therefore ideally suited to study risk factors and onset of RLS. This study aims to estimate the prevalence of RLS in a population of healthy Danes and identify associated sociodemographic, socioeconomic and lifestyle characteristics. Further, we plan to examine whether reduced iron stores, likely to be caused by blood donations, are associated with occurrence of RLS.

1. Methods

1.1. Data

The present study collected data from the Danish Blood Donor Study (DBDS), which is an ongoing epidemiological cohort study and biobank that currently comprises data on more than 100,000 healthy blood donors between the ages of 18 and 67 years. This corresponds to a response rate of 95% of all invited donors [11]. The DBDS is built upon the infrastructure of the Danish blood banks, as data is collected through an extensive dynamic digital questionnaire that is administered to donors upon donation (www.dbds.dk) where whole blood and plasma samples are also collected. Individual donors visiting a Danish blood bank for their second or subsequent blood donations are informed about DBDS and are invited to participate after providing written informed consent. With the size of the cohort and the range of collected information, DBDS represents a unique opportunity to study RLS in a large population of otherwise healthy individuals.

1.1.1. Ethics statement

Oral and written informed consent was obtained from all participants. The study was approved by The Scientific Ethical Committee of Central Denmark (M-20090237). Additionally, the biobank and research database have been approved by the Danish Data Protection Agency (2007-58-0015).

1.1.2. Identifying RLS among blood donors

RLS within the blood donor population was identified using the Cambridge-Hopkins RLS-questionnaire (CH-RLSq), which is a questionnaire containing 10 items that has been validated in several population settings (diagnostic sensitivity 87.2% and specificity 94%) [12,13]. CH-RLSq is the only patient-completed questionnaire validated for identification of RLS in general populations [14]. The CH-RLSq was translated into Danish by multiple people independently of each other. Subsequently, the versions translated into Danish were translated back to English by other people who had no knowledge of the content in the original English version of the CH-RLSq. Finally, all translations were compared and the final Danish version was completed and administered to the donors. Experience with using this scale has led to concerns about possible misclassification of RLS due to misinterpretation of item 8 in the CH-RLSq. Item 8 reads: “Will simply changing leg position by itself once without continuing to move usually relieve these feelings?” People who answer “usually relieve” to this question are, according to the RLS-scoring scheme, classified as not affected by RLS. However, it is reported that RLS-sufferers actually do experience some temporary, short-lived, relief when changing position without further movement. Further, there are problems related to translation of this specific item. For both of these reasons item 8 is considered to be susceptible to misunderstanding. Such misclassification is likely to cause an underestimation of the prevalence of RLS and thereby also of the associated factors. In a data sample of 128 UK blood donors diagnosed with RLS by means of the validated Hopkins Diagnostic Telephone Interview (HTDI) (diagnostic sensitivity 90% and specificity 91%) [15], which is considered the gold standard of RLS diagnostic tools [16], we found that 15% answered “usually relieve” to item 8 in the CH-RLSq. Furthermore, we found that 62.5% of the people who answered “does not usually relieve” to item 8 received an RLS-diagnosis in the HTDI. These data made us conduct additional analyses of the RLS prevalence, and associated factors, with item 8 omitted from the scale. These analyses are presented next to the findings from the complete CH-RLSq in Tables 1–3. Moreover, to eliminate individuals solely with muscle cramps as RLS cases, participants who answered yes to item 9a (“Are these feelings ever due to muscle cramps?”) were required to also answer no to item 9b (“if so, are they always due to leg cramps?”) to classify with RLS.

1.1.3. Reduced iron level

Circulating ferritin reflects the level of tissue iron stores and previous studies suggest that a ferritin level less than 30 ng/ml optimally identifies blood donors with low iron stores [17]. Therefore, we defined a reduced iron level as ferritin levels less than 30 ng/ml. To ensure complete assessment of all participants with potentially reduced iron levels, we also investigated ferritin levels less than 40 ng/ml. The link between reduced iron store levels and RLS among the participants was only examined for a subgroup, as we only had plasma ferritin measurements available for 4048 participants (2027 men and 2021 women). The ferritin levels were measured within 14 days of inclusion into DBDS and RLS assessment (ie, mid-April 2015 to mid-May 2016). To ensure statistical power, these analyses were conducted separately from the remaining analyses. For the entire study population ($N = 13,448$) we examined the number of donations for the past three years as a proxy measure for iron deficiency because this factor has previously been found to be the strongest predictor of iron deficiency (ferritin level <15 ng/ml) in the DBDS population [6].

1.1.4. The digital questionnaire

Part of the data analyzed in the present study was collected from the digital questionnaire filled out by the DBDS participants upon inclusion. The data consisted of self-reported information on sex,

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