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Original Article

Restless legs syndrome in dialysis patients: a meta-analysis

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ABSTRACT

Background: Restless legs syndrome (RLS) occurs frequently in dialysis patients. However, it remains elusive regarding the risk factors for RLS onset in dialysis patients.
Methods: A meta-analysis was performed to investigate the association between clinical measures (age, gender, diabetes mellitus or DM etc.) and RLS in dialysis patients. We searched electronic databases from January 1990 to February 2014 to identify studies that met inclusion criteria. Either a fixed-effects or, in the presence of heterogeneity, a random-effects model was used to calculate the pooled odds ratios (ORs)/standard mean differences (SMDs) and their corresponding confidence intervals (CIs).
Results: Twenty-three studies were included in this study. Dialysis patients with RLS demonstrated significantly higher OR of DM compared with non-RLS in Asians (OR: 1.238, 95% CI: 1.032–1.484, $P = 0.021$). Dialysis patients with RLS showed markedly lower level of hemoglobin (Hb)/iron compared with non-RLS in overall populations/Caucasians (SMD: –0.178/–0.104, 95% CI: –0.352/–0.206 to –0.004/–0.002, $P = 0.045/0.045$; SMD: –0.283/–0.158, 95% CI: –0.552/–0.304 to –0.013/–0.012, $P = 0.04/0.034$). No differences of female populations, age, duration of dialysis, body mass index (BMI), blood urea nitrogen (BUN), creatinine, albumin, phosphorus, parathyroid hormone (PTH), and calcium were observed between dialysis patients with RLS and non-RLS in overall populations, Caucasians and Asians. No evidence of publication bias was observed.
Conclusions: Our findings indicate that dialysis patients with DM are nearly 24% more susceptible to RLS in Asians. Decreased Hb/iron is a risk factor for RLS onset in dialysis patients in overall populations including Caucasians.

1. Introduction

Restless legs syndrome (RLS), a common sleep-related movement disorder, is characterized by unpleasant leg sensations and an urge to move the legs [1]. RLS frequently occurs during rest and at night and improves upon movement [2]. It is associated with a significantly lower quality of life and even affects life expectancy [3]. RLS can be idiopathic or secondary to other conditions, such as pregnancy, iron deficiency and end-stage renal disease (ESRD) [4]. It has been indicated that the prevalence of RLS is higher in dialysis than in predialysis or in transplanted patients [5].

Occurrence of RLS in dialysis patients can aggravate the burden and cause great inconvenience. On the other hand, the presence of RLS might also indicate incorrect dialysis treatment. Hence, identification of the risk factors for the onset of RLS in dialysis patients is necessary for improving life quality.

In the past decades, various studies [5–27] have been conducted to focus on the contributing factors for RLS in dialysis patients. Being female, longer duration of dialysis, and iron deficiency have been considered risk factors for RLS among dialysis patients [1]. However, certain studies [5,9,14,27] yielded inconsistent results. Furthermore, racial and geographic differences may also influence the prevalence of RLS in dialysis patients. Identification of the risk factors may provide better guidance for the time of dialysis in patients. A previous review by Kavanagh et al. [1] showed that optimization of iron and hemoglobin (Hb) levels with erythropoietin and iron appears to be beneficial to dialysis patients. However, pooled quantitative analysis was not performed in this review, which made these results less robust.

For answering the urgent clinical questions, it is more appropriate to synthesize the available research results. Meta-analysis is a systematic method to identify, evaluate, synthesize, and combine the results of associated studies to provide quantitative results; this has been applied increasingly in clinical studies with the aim of providing robust conclusions [28]. However, it has some limitations in integrating the results from different studies, due to the diverse nature of the studies, such as the study design, sample sizes, and populations [29]. Subgroup and regression analyses have been performed to identify the differences in study outcomes [30]. In terms

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of the types of data mentioned above, meta-analysis is an appropriate way to summarize the available evidence to achieve a more reliable conclusion. We therefore performed this meta-analysis to identify the potential risk factors for the susceptibility to RLS of dialysis patients.

2. Methods

2.1. Search strategy

We conducted a search of published studies that reported the potential risk factors [age, gender, diabetes mellitus (DM), duration of dialysis, body mass index (BMI), Hb blood urea nitrogen (BUN), creatinine, albumin, phosphorus, iron, parathyroid hormone (PTH), and calcium] of both RLS and non-RLS in dialysis patients from January 1990 to February 2014 using PubMed, Embase, and Cochrane databases. The search terms were as follows: (1) dialysis, hemodialysis, peritoneal dialysis, chronic kidney disease, end-stage renal disease; (2) age, gender, male, female, diabetes mellitus, DM, duration, body mass index, BMI, hemoglobin, Hb, blood urea nitrogen, BUN, creatinine, albumin, phosphorus, iron, parathyroid hormone, PTH, calcium; and (3) risk, prevalence. The diagnostic criteria of RLS were retrieved from the International RLS Study Group (IRLSSG) [31], International Classification of Sleep Disorders (ICSD) [32], and CHOICE Health Experience Questionnaire (CHEQ) [33]. Reference lists of extracted publications were also reviewed. If the same participants were enrolled in more than one study, we recruited the study with the complete analysis.

2.2. Study selection

We performed an initial screening of titles or abstracts followed by a full-text review. Studies were considered eligible if they met the following criteria: (1) the study design was a cohort, case-control, cross-sectional or case-only design; (2) the study populations were RLS and non-RLS patients in dialysis; (3) the outcome of interest was one or more of the potential risk factors (age, gender, DM, duration of dialysis, BMI, Hb, BUN, creatinine, albumin, phosphorus, iron, PTH, and calcium); and (4) odds ratio (OR)/standard mean difference (SMD) and the corresponding 95% confidence interval (CI) (or data to calculate them) for these factors between RLS and non-RLS patients in dialysis were reported.

2.3. Data extraction

Study characteristics were recorded as follows: first author's surname; year of publication; ethnicity; duration of dialysis; age; number of RLS and non-RLS; number of female population and DM; the levels of BMI, Hb, urea, creatinine, albumin, phosphorus, iron, PTH, and calcium in dialysis patients with and without RLS. Two authors independently performed the literature search, study selection, and data extraction with any disagreement resolved by discussion.

2.4. Statistical analyses

Odds ratio was used to measure the association between female populations/DM and RLS risk in dialysis patients across studies. SMD was used to measure the differences in age, duration of dialysis, BMI, Hb, BUN, creatinine, albumin, phosphorus, iron, PTH, or calcium among RLS and non-RLS in dialysis patients. Heterogeneity of ORs/SMDs across studies was tested using the Q-statistic at the significance level of $P < 0.05$. The I^2-statistic, a quantitative measure of inconsistency across studies, was also calculated. Significant heterogeneity was indicated at the value of $I^2 > 50\%$. The combined risk estimates were calculated using either fixed-effects models or, in the presence of heterogeneity, random-effects models. Sensitivity analysis was performed in Caucasians and Asians. Subgroup analysis was performed in the enrolled studies with RLS criteria consistent with four diagnostic criteria proposed by the IRLSSG. Potential publication bias was assessed by Begg's test and Egger's test at the $P < 0.05$ level of significance when the number of the studies included was >10. All analyses were performed using STATA version 12.0 (Stata Corp., College Station, TX, USA). $P < 0.05$ was considered statistically significant, except where otherwise specified.

3. Results

3.1. Literature search

In all, 156 relevant citations were retrieved from the PubMed, Embase, and Cochrane databases. Most of these papers were excluded after the first screening in terms of titles or abstracts, mainly because they were not related to RLS or dialysis. After full-text review of 31 papers, eight studies were excluded because they did not state the risk factors of RLS in dialysis. Finally, 23 studies [5–27] were included in the meta-analysis. A flow chart showing the study selection is presented in Fig. 1.

3.2. Study characteristics

The characteristics of the 23 recruited studies are listed in Table 1. These studies were published between 1991 and 2013. They were conducted among Caucasian and Asian populations. The sizes of studies ranged from 83 to 17,448 subjects.

3.3. Meta-analysis

There were no marked differences in age, female populations, duration of dialysis, BMI, BUN, creatinine, albumin, phosphorus, PTH, or in calcium between dialysis patients with RLS and without RLS in overall populations, Caucasians, and Asians (Table 2). No evidence of publication bias was observed in age for overall populations (Begg, $P = 0.727$; Egger, $P = 0.82$), female populations for overall populations/Caucasians (Begg, $P = 0.807/0.796$; Egger, $P = 0.49/0.512$), and creatinine/albumin/phosphorus for overall populations (Begg, $P = 0.392/0.784/0.783$; Egger, $P = 0.703/0.574/0.398$). DM was associated with a significantly higher risk of RLS in Asian dialysis patients (OR, 1.238; 95% CI, 1.032 to 1.484; $P = 0.021$) (Table 2, Fig. 2). Dialysis patients with RLS showed a markedly lower level of Hb than

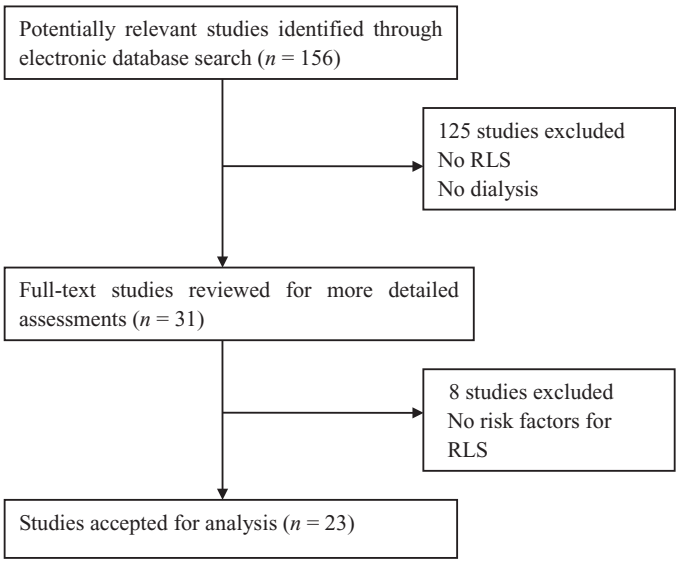

Fig. 1. Flow chart of study selection. RLS, restless legs syndrome.