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Original Article

Restless legs syndrome in hemodialysis patients: an epidemiologic survey in Greece

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ABSTRACT

Background: Restless legs syndrome (RLS) is a sensorimotor disorder characterized by an uncontrolled need to move extremities accompanied by unpleasant sensations, which frequently leads to sleep disturbances. In hemodialysis (HD) patients, the previously reported RLS prevalence varied enormously, between 6% and 60%. In our study, we investigated the RLS prevalence in HD patients for the first time in Greece.

Methods: A continuous sample of HD patients was studied between January and September of 2010 in six dialysis units in Greece. RLS diagnosis was based on the essential clinical criteria of the International RLS Study Group (IRLSSG). The standardized incidence ratio (SIR) for RLS in HD patients was calculated in comparison to data from a recent survey of the general population in Greece.

Results: In our study of 579 HD patients in Greece (236 women; mean age, 65 ± 13 years), the prevalence of RLS was elevated in comparison to the general population (26.6% vs 3.9%), with an SIR of 5.4 (95% confidence interval [CI], 4.6–6.3). In the fully adjusted model, the risk for RLS in HD patients was reduced in older age (odds ratio [OR], 0.98 [95% CI, 0.96–0.99]) and increased in women (OR, 1.60 [95% CI, 1.05–2.43]) in cases with elevated levels of β_2 microglobulin (OR, 1.15 [95% CI, 1.01–1.32]) and intact parathormone (iPTH) (OR, 1.30 [95% CI, 1.08–1.56]).

Conclusion: A high RLS prevalence was recorded in a large HD population in Greece, clearly suggesting the need for enhanced awareness of RLS in nephrology. The RLS risk was increased in women and in younger HD patients as well as in those with elevated β_2 microglobulin and iPTH levels.

1. Introduction

Restless legs syndrome (RLS), or Willis-Ekbom disease [1,2], is a neurologic sensorimotor disorder characterized by an urgent uncontrolled need to move the extremities accompanied or caused by peculiar unpleasant sensations (paresthesias) in these extremities. Symptoms are likely to appear or worsen at rest; are temporarily relieved by movement of the affected limb; and are more severe in the evening or at night, frequently leading to sleep disturbances [3].

RLS typically is an idiopathic disorder (primary RLS), but it also may accompany various medical conditions (secondary RLS), including pregnancy, iron depletion, peripheral neuropathy, radiculopathy, and rheumatoid arthritis. An additional frequent form of secondary RLS occurs in chronic kidney disease and end-stage renal disease (ESRD), which is called uremic RLS [4]. The diagnosis of RLS is based on the International RLS Study Group (IRLSSG) consensus from 2003, which defined the four essential diagnostic criteria [3]. The RLS prevalence in the general population varies between 0.1% and 15% [5–10]. It is lowest in Asian populations

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[7] and southeast Europe [5,11] in comparison to other European countries [9]. In hemodialysis (HD) patients, the RLS prevalence reported in previous studies varies between 6% and 60% [12–18]. This large variation may be dependent on the heterogeneity of the diagnostic tools used before the 2003 consensus meeting and the characteristics of the study population examined in each study.

The aim of our study was to estimate the RLS prevalence in a large number of Greek patients with ESRD on HD treatment and to evaluate the association of RLS with parameters related to uremic status and quality of dialysis, renal anemia, iron status, cachexia-inflammation, and bone metabolism.

2. Methods

We conducted a cross-sectional study between January and September of 2010 in six dialysis units in central Greece (2 units) and northern Greece (4 units). We included all ESRD patients on HD treatment (for $\geqslant$2 times/week) for at least 3 months; however, we excluded patients who were unable to communicate, unable to give informed consent, and unable to visit the unit during the investigation period due to hospitalization or vacation. All participants provided informed consent. The study was approved by the Ethics Review Board of the University Hospital of Larissa.

All participants were investigated by interviews and by reviewing their medical records. Medical doctors (AV) and (ED), both trained in RLS clinical diagnosis by an expert neurologist (GMH), conducted the screening interviews. The Greek version of the four essential IRLSSG clinical criteria, which has been validated in previous studies, was implemented as a screening tool [5]. Patients were included when all four criteria were fulfilled, a diagnosis was confirmed, and RLS severity was evaluated according to the IRLSSG rating scale (Greek version) during a personal interview conducted by an RLS expert [5,19]. According to the IRLSSG rating scale, severity was classified as mild (<11 on the IRLSSG rating scale), moderate (11–20), severe (21–30), and very severe (31–40) [20].

Additionally, the personal and family history of RLS was explored in all patients with RLS; for example, patients with RLS were asked about the existence of symptoms before beginning HD treatment and RLS diagnosis in at least one of their first-degree relatives (free of nephropathy).

The medical records including relevant clinical and laboratory data from all of the patients were recorded as shown in Tables 1 and 3 [4]. Routine laboratory methods were implemented for measurements of hematologic and biochemical parameters which were registered in the study. In particular, the high-sensitivity C-reactive protein (reference range, 0.1–3.0 mg/L) and the β_2-microglobulin levels in serum (reference range, 0.8–3.0 mg/L) were determined by immunoturbidimetric assays with the COBAS INTEGRA® 400 plus system (Roche Diagnostics, Indianapolis, IN, USA). The iPTH levels were determined by a chemiluminescence immunoassay with the Elecsys® System (Roche Diagnostics, Indianapolis, IN, USA).

2.1. Statistical analysis

The data for continuous variables were expressed as the mean value and standard deviation unless otherwise denoted. The frequencies of categorical variables were presented as percentages (or ratios) with 95% confidence intervals (CIs) as appropriate. The normality of continuous variables was tested by the Kolmogorov–Smirnov test. Pairwise comparisons of continuous variables were performed with the *t* test or the Mann–Whitney *U* test for unpaired data, as appropriate. The frequencies of categorical variables were compared with the χ^2 test and Fisher exact test. As a risk estimate, the odds ratio (OR) with its respective 95% CI was calculated. An interrater reliability analysis was performed using the κ statistic to determine consistency among raters of the four screening questions (Greek version) [21].

The standardized incidence ratio (SIR) for RLS in HD patients was calculated using data from a recent survey of the general population in central Greece [5]. The observed numbers of RLS cases among patients on HD were compared with the expected numbers derived from the prevalence in the general population in Greece. Expected numbers of RLS were calculated based on age-specific prevalence rates (7 strata) of the general population in central Greece determined in the above survey [5]. Then the total numbers of observed cases were divided by the corresponding total expected number to obtain the SIR, and a 95% CI was calculated under the assumption that the number of incidences had a Poisson distribution [22,23].

Potential determinants of the RLS status (dichotomous variable) were investigated with a binary logistic regression model. Only cases with a full dataset were used for this analysis. The following covariates were included in the model: age (years), gender (men/women), duration of dialysis (months), dialysis mode (hemodialysis or hemodiafiltration), body mass index (kg/m^2), serum urea before HD (mg/dL), urea reduction ratio (URR, %), Kt/V, β_2 microglobulin (mg/L), C-reactive protein (mg/L), albumin (g/dL), hemoglobin (g/dL), serum iron (μg/dL), ferritin (ng/mL), transferrin (mg/dL), transferrin saturation (%), calcium (mg/dL), phosphorus (mg/dL), calcium $\times$ phosphorus product (mg^2/dL^2), and iPTH (arbitrary units). The RLS status was the dependent variable (outcome) in the model, and the OR was calculated as the antilogarithm of the β coefficient of each independent variable (covariate). The iPTH was first transformed to a categorical variable with 4 strata, namely the quartiles of its serum values (arbitrary units), and then included as a dummy variable in the model. The goodness-of-fit of the binary logistic model was assessed by the Hosmer–Lemeshow test, and colinearity was evaluated using the colinearity matrix.

Overall, statistical analyses were performed using the Statistic Package for Social Sciences 13.0 (SPSS® version 13.0) for Windows (SPSS Inc., Chicago, IL, USA). A level of $P < .05$ was considered to be statistically significant.

3. Results

Overall the epidemiologic survey included 579 patients (236 women; mean age, 65 ± 13 years) with ESRD treated with long-term HD (Table 1). Among the HD patients who were informed about the study, none denied participation but 24 patients were not included for reasons irrelevant to the study protocol. The interrater reliability for the two raters (AV and ED) was found to be nearly perfect (κ = 0.96 [95% CI, 0.67–1.24]).

The prevalence of RLS in HD patients found in our study was 26.6% (154/579). The difference in RLS prevalence between women (30.1% [71/236]) and men (24.2% [83/343]) was not statistically significant (P = .126; Table 1). In comparison to the general population in Greece [5], the RLS prevalence in HD patients was significantly elevated (26.6% vs 3.9%), with a standardized incidence ratio of 5.4 (4.6–6.3) (Table 2).

HD patients with RLS were significantly younger compared to patients without RLS (61 ± 13 vs 66 ± 13 years, $P < 0.001$; Table 1). However, duration of HD treatment (months) and body mass index (kg/m^2) did not differ between HD patients with and without the syndrome. The primary causes of chronic kidney disease in our patients are shown in Table 1. Peripheral neuropathy, as registered in the medical records, was found in 34 (22.1%) HD patients with RLS and in 52 (12.2%) patients without RLS (P = .005).