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Association between predialysis hypermagnesaemia and morbidity of uraemic restless legs syndrome in maintenance haemodialysis patients: a retrospective observational study in Zhejiang, China

Yi Yang,[1] Hongying Ye,[1,2] Qien He,[1,3] Xiaohui Zhang,[1,4] Biying Yu,[5] Jingjuan Yang,[1,5] Jianghua Chen[1]

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For numbered affiliations see end of article.

Correspondence to
Dr Yi Yang; yangyixk@zju.edu.cn

ABSTRACT

Objective The aim of the present study was to determine whether the predialysis serum magnesium level was associated with morbidity of uraemic restless legs syndrome (RLS) in maintenance haemodialysis patients.

Design A retrospective observational study of morbidity of uraemic RLS was conducted.

Setting Patients on maintenance haemodialysis three times a week.

Participants We reviewed 578 patients receiving maintenance haemodialysis for >1 year as our cohort.

Outcome measures Uraemic RLS was diagnosed according to International RLS Study Group criteria, and hypermagnesaemia was defined as serum magnesium level >1.02 mmol/L.

Results The prevalence of uraemic RLS was 14.4% in our study cohort. Univariate analysis indicated that patients with uraemic RLS differed significantly from non-RLS ones in certain demographic and clinical characteristics, including younger age, longer dialysis duration, higher serum parathyroid hormone level and higher prevalence of predialysis hyperphosphataemia and hypermagnesaemia. Binary logistic-regression model analysis indicated that predialysis hypermagnesaemia was independently associated with uraemic RLS and conferred an increase in morbidity of the syndrome (OR=2.024; 95% CI 1.160 to 3.532; p=0.013). Moreover, we found that dialysis duration and predialysis hyperphosphataemia were independently associated with morbidity of uraemic RLS.

Conclusions Our data indicated that the predialysis serum magnesium level was associated with morbidity of uraemic RLS in maintenance haemodialysis patients and that predialysis hypermagnesaemia might serve as an independent risk factor for the syndrome.

Strengths and limitations of this study

- This is the first study on the association between predialysis hypermagnesaemia and morbidity of uraemic restless legs syndrome (RLS) in maintenance haemodialysis patients in Zhejiang, China.
- Nephrologists and neurologists determined a diagnosis of uraemic RLS to avoid diagnosis bias.
- The retrospective study design and the small sample size decreased the power of the conclusions.

INTRODUCTION

Uraemic restless legs syndrome (RLS) is one of the most important types of secondary RLS, contributing to further impairments in the already diminished quality of life and health status of the patient with uraemia.[1] Uraemic RLS is very common among patients undergoing maintenance haemodialysis, according to previous studies.[2 3] Along with the growing interest in RLS over the past decade, abundant evidence associated with this syndrome has been coming to light. However, the pathophysiology of uraemic RLS and the roles of its potential risk factors are not fully understood.

Various changes in laboratory parameters that are common in maintenance haemodialysis patients, including anaemia, low serum iron and protein malnutrition have been reported as potential causes of uraemic RLS.[4–6] Electrolyte disturbances, such as low or high serum calcium, phosphorus and parathyroid hormone (PTH) levels, have also been cited as important risk factors.[7] Unfortunately, the results of previous studies on aetiological risk factors for uraemic RLS remain controversial.

Magnesium is the fourth most abundant cation in the human body and the second most abundant in the intracellular space, playing a pivotal role in vital cellular function.[8 9] The importance of this mineral in particular has been recognised due to its effect

on the cardiovascular and neuromuscular systems.[10–12] It has been reported that serum magnesium concentration is inversely related to both PTH and fibroblast growth factor 23 (FGF23) levels, meaning that it is involved in the regulation network of mineral and bone disorders in the disease state.[13 14] Therefore, magnesium is essential for electrolyte stabilisation in maintenance haemodialysis patients. Furthermore, recent data indicate a significant relationship between serum magnesium and muscle quality in maintenance haemodialysis patients.[15] Theoretically, magnesium disturbance might be a candidate aetiological factor for uraemic RLS. However, magnesium receives only scant attention from most clinicians caring for dialysis patients, and data on the potential relationship between magnesium disturbance and uraemic RLS are very scarce.

Here, we retrospectively studied a cohort of maintenance haemodialysis patients to determine whether predialysis serum magnesium level was associated with morbidity of uraemic RLS in these patients.

MATERIALS AND METHODS

Patient selection

We screened all of the patients who were receiving maintenance haemodialysis at four haemodialysis centres in Zhejiang Province, China, on 10 July 2018. Those who had been receiving dialysis for >1 year were recruited as the cohort of the present study.

Patient involvement

No patients were directly involved in the selection of the outcome measures, design and implementation of the study, or interpretation of the results. Patients can assess results of the hospital's studies via Internet website and posters on the hospital walls.

Patient data

All of the patient data were abstracted from medical records, as well as from the linked clinical inspection and blood purification databases at the clinic hospitals. We collected the following demographic and clinical information from the patients during screening: age, gender, premorbidity of type II diabetes or hypertension or secondary hyperparathyroidism (SHPT), dialysis duration, body mass index (BMI) and haemodialytic modality. We also collected the following predialysis laboratory parameters from the 12 months before screening to calculate means: Kt/V, haemoglobin (Hb) concentration, serum ferritin (SF) level, transferrin saturation (TFS), serum albumin (Alb) concentration, serum PTH level, serum phosphorus concentration and serum magnesium level. Serum electrolyte level was tested every 3 months using an ABL800 FLEX Analyzer (Radiometer Medical ApS, Brønshøj, Denmark). All of the patients received 4-hour intermittent haemodialysis 3 times per week. Dialysate regimens are shown in table 1.

Table 1 Dialysate regimens adopted in the four dialysis centres

Dialysate composition	Prescription 1 (mEq/L)	Prescription 2 (mEq/L)	Prescription 3 (mEq/L)
Sodium	136–140	136–140	136–140
Potassium	2.0	2.0	3.0
Calcium	2.5	3.0	3.0
Magnesium	1.0	1.0	1.0
Chlorine	110	110	110
Bicarbonate	32–34	32–34	32–34

Variables

Uraemic RLS was diagnosed jointly by nephrologists and neurologists based on International RLS Study Group (IRLSSG) criteria, including essential and supportive criteria, as well as associated features of RLS. According to the colorimetric method, hyperphosphataemia as serum phosphorus level >1.51 mmol/L, hypermagnesaemia as serum magnesium level >1.02 mmol/L and hypoalbuminaemia as Alb concentration <40 g/L.

Statistical analysis

We conducted statistical analysis using SPSS software V.23.0 (SPSS. P<0.05 was considered to be statistically significant. We performed a univariate comparison of variables between two groups using an unpaired t-test for continuous variables and a χ^2 test or Fisher's exact test for categorical variables. Binary logistic regression analysis was applied to identify the independent contributions of risk factors to prediction of morbidity in uraemic RLS. When constructing the multivariate model, we used univariate factors with p<0.2. We used ORs with 95% CIs to gauge the association between the independent variables and the dependent variable.

RESULTS

We reviewed a total of 578 patients receiving maintenance haemodialysis for the present study, of whom 83 were diagnosed with uraemic RLS; therefore, the syndrome's prevalence was 14.4% in our study cohort. Baseline demographics and clinical characteristics of the patients are summarised in table 2. Mean age±SD for patients in the cohort was 59.45±14.06 years, and 363 (62.8%) patients were male. Mean dialysis duration±SD was 3.55±3.24 years; 274 (47.4) patients were using dialysate with calcium concentration of 3.0 mEq/L, while 304 patients were using dialysate with calcium concentration of 2.5 mEq/L; 206 (35.6%) patients were receiving high-flux haemodialysis (ultrafiltration coefficient of the dialyser >25 mL/mm Hg/hour), while 272 (47.1%) patients were receiving low-flux haemodialysis and weekly haemodiafiltration. Univariate analysis indicated no significant differences between patients with uraemic RLS and non-RLS ones sharing certain demographic and clinical characteristics, including gender, premorbidity of type II diabetes

Table 2 Baseline demographics and clinical characteristics of patients

Characteristics	Patients (n=578)	RLS patients (n=83)	Non-RLS patients (n=495)	P value
Male sex (%)	363 (62.8)	46 (55.4)	317 (64.0)	0.133
Mean age (years)	59.45±14.06	56.39±11.73	59.97±14.36	0.014
Premorbidity				
Type II diabetes (%)	230 (39.8)	27 (32.5)	203 (41.0)	0.144
Hypertension (%)	260 (45.0)	35 (42.2)	225 (45.5)	0.578
SHPT (%)	485 (83.9)	70 (84.3)	415 (83.8)	0.909
Dialysis duration (years)	3.55±3.24	5.44±4.56	3.24±2.85	<0.001
Dialysate calcium concentration of 3.0 mEq/L (%)	274 (47.4)	39 (47.0)	235 (47.5)	0.934
BMI	21.98±3.44	21.85±3.43	22.00±3.44	0.714
Haemodialytic modality				
High-flux haemodialysis (%)	206 (35.6)	25 (30.1)	181 (36.6)	0.257
HDF weekly (%)	272 (47.1)	43 (51.8)	229 (46.3)	0.349

P value, RLS cohort versus non-RLS cohort.
BMI, body mass index; HDF, haemodiafiltration; RLS, restless legs syndrome; SHPT, secondary hyperparathyroidism.

or hypertension or SHPT, BMI or haemodialytic modality. Meanwhile, compared with non-RLS patients, those with uraemic RLS were younger and had undergone dialysis for a longer period of time.

We calculated and compared patients' serum electrolyte levels during the 12 months before study cohort screening. Our data indicated patients with uraemic RLS had significantly higher predialysis serum phosphorus and magnesium levels compared with non-RLS patients (figure 1). Other patient laboratory parameters from the year before the screening, along with prevalence of electrolyte disturbance, are summarised in table 3. There were no significant differences in Hb, SF, TFS, Kt/V or prevalence of hypoalbuminaemia between the uraemic RLS and non-RLS groups. Compared with the non-RLS patients, those with uraemic RLS had significantly higher levels of predialysis hyperphosphataemia, hypermagnesaemia and serum PTH.

The presence or absence of predialysis hypermagnesaemia and other univariate factors with p values <0.2 are shown in tables 2 and 3. These included male sex, age, premorbidity of type II diabetes, dialysis duration, serum PTH level and presence or absence of predialysis hypoalbuminaemia and hyperphosphataemia. Binary logistic regression including these factors indicated that predialysis hypermagnesaemia was independently associated with morbidity of uraemic RLS. Patients who had predialysis hypermagnesaemia had higher morbidity of uraemic RLS than patients who did not have it (OR=2.024; 95% CI 1.160 to 3.532; p=0.013; table 4). Moreover, we found that dialysis duration and predialysis hyperphosphataemia were independently associated with morbidity of uraemic RLS.

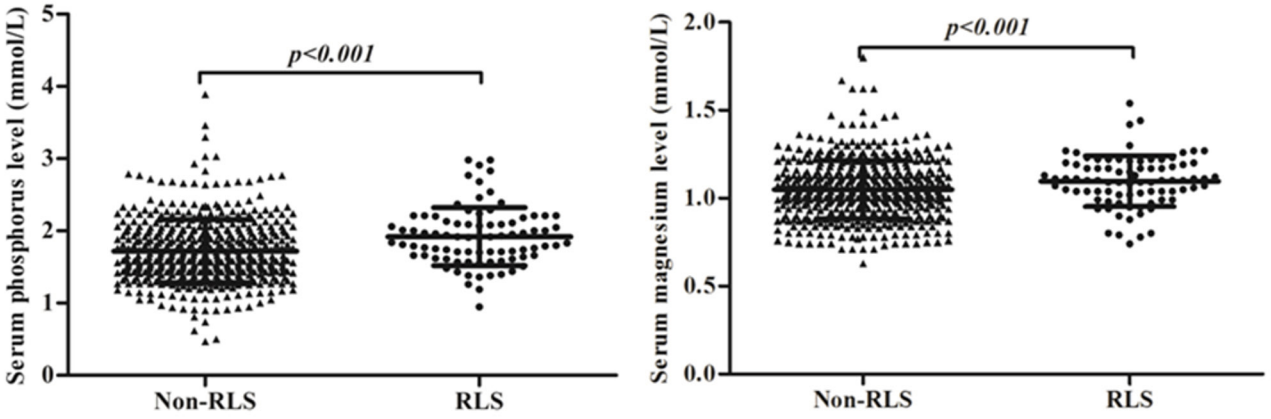

Figure 1 Patients with uraemic RLS had significantly higher predialysis serum calcium, phosphorus and magnesium levels compared with non-RLS patients. RLS, restless legs syndrome.

Table 3 Predialysis laboratory parameters of the patients during the 12 months before screening

Characteristics	Patients (n=578)	RLS patients (n=83)	Non-RLS patients (n=495)	P value
Hb concentration (g/L)	99.40±14.20	98.14±13.26	99.62±14.36	0.380
SF level (µg/L)	176.72 (95.14–349.59)	167.16 (89.56–388.15)	177.48 (95.38–342.34)	0.971
TFS (%)	33.02±13.11	33.08±12.97	32.69±13.98	0.807
Kt/V	1.30±0.24	1.29±0.22	1.31±0.25	0.545
Serum PTH level (ng/L)	227.00 (123.35–386.73)	377.30 (230.80–676.30)	214.30 (117.50–339.50)	<0.001
Hypoalbuminaemia (%)	370 (64.0)	47 (56.6)	323 (65.3)	0.130
Hyperphosphataemia (%)	389 (67.3)	72 (86.7)	317 (64.0)	<0.001
Hypermagnesaemia (%)	331 (57.3)	62 (74.7)	269 (54.3)	0.001

Hypoalbuminaemia, serum albumin concentration <40 g/L; hyperphosphataemia, serum phosphorus level >1.51 mmol/L; hypermagnesaemia, serum magnesium level more than >1.02 mmol/L.
Hb, haemoglobin; PTH, parathyroid hormone; RLS, restless legs syndrome; SF, serum ferritin; TFS, transferrin saturation.

DISCUSSION

Uraemic RLS is common in the end-stage renal disease (ESRD) population, and the prevalence of the disease reaches approximately 30% of the ESRD population (range 7%–45%) based on the IRLSSG diagnosis criteria.[16] The prevalence of uraemic RLS was 14.4% in our study cohort. In a clinical setting, it is difficult to diagnose uraemic RLS accurately because IRLSSG criteria are mainly based on answers to various patient interview questions, and many patients experience difficulty in properly describing their symptoms.[17] Furthermore, there are not yet any specific diagnostic criteria exclusive to the diagnosis of uraemic RLS.[18] Therefore, diagnosis bias might be a factor, especially for patients with uraemic. In the present study, nephrologists and neurologists determined a diagnosis of uraemic RLS to avoid diagnosis bias. The prevalence of uraemic RLS in the present study was relatively low, which might have been partly due to the strict diagnosis strategy adopted.

Table 4 Variables included in multivariable logistic regression analysis and HRs

Variables	OR (95% CI)	P value
Male sex (%)	0.652 (0.391 to 1.087)	0.101
Mean age (years)	0.996 (0.977 to 1.016)	0.715
Premorbidity		
Type II diabetes (%)	1.403 (0.825 to 2.386)	0.211
Dialysis duration (years)	1.144 (1.065 to 1.229)	<0.001
Serum PTH level (ng/L)	1.001 (1.000 to 1.001)	0.011
Hypoalbuminaemia (%)	1.433 (0.844 to 2.434)	0.183
Hyperphosphataemia (%)	2.597 (1.295 to 5.208)	0.007
Hypermagnesaemia (%)	2.024 (1.160 to 3.532)	0.013

Hypoalbuminaemia, serum albumin concentration <40 g/L; Hyperphosphataemia, serum phosphorus level >1.51 mmol/L; hypermagnesaemia, serum magnesium level more than >1.02 mmol/L .
PTH, parathyroid hormone.

The precise pathogenic mechanism responsible for uraemic RLS is still unclear. Dopaminergic system disturbance is widely hypothesised to be part of the mechanism for idiopathic RLS and also considered the most important treatment target for that syndrome.[19] In the presence of uraemia, the mechanism is quite different and more complex. Some factors exclusively associated with haemodialysis itself might play important roles in the pathogenic mechanism of uraemic RLS, including anaemia, low serum iron, protein malnutrition, electrolyte disturbance, haemodialytic modality and haemodialytic adequacy.[2 3 20] However, the associations between those risk factors and uraemic RLS remain controversial. Therefore, it is interesting to carry out the study for the topic. Our data, which indicated that predialysis hypermagnesaemia was an independent risk factor for morbidity of uraemic RLS, may potentially shed light on the aforementioned risk factors.

Magnesium is essential for health and is involved in a great number of crucial physiological functions, but unfortunately it remains the neglected cation in maintenance haemodialysis patients.[8] In contrast with other electrolytes such as potassium or calcium, clinicians rarely regulate magnesium concentration in dialysate. Magnesium ions serve as cofactors of about 300 enzymes and play important roles in energy metabolism, gene expression and molecule synthesis, particularly in bone growth and maintenance of neuromuscular excitability.[21] Previous study has found that the excitability of peripheral motoneurons contributed to the pathophysiology of RLS.[22] It has been reported that serum magnesium is significantly associated with muscle quality in maintenance haemodialysis patients.[15] It might suggest that the excitability of peripheral motoneurons may involve in the incidence of uraemic RLS.

The basic biological function of magnesium might explain why hypermagnesaemia was associated with morbidity of uraemic RLS in our study. Another possible explanation for the relationship between hypermagnesaemia and uraemic RLS might be the role of magnesium

in electrolyte balance. Therefore, variations in serum magnesium concentration may cause other type of electrolyte disturbances, including calcium–phosphorus metabolism via the PTH–FGF23 pathway.[13 14] In this study, we also found that hyperphosphataemia was associated with RLS, which was consistent with the previous study.[23] FGF23 is a key regulator of vitamin D and phosphorus metabolism and can participate in bone metabolism by regulating blood phosphorus, vitamin D, PTH and other bone metabolism-related factors. Serum magnesium might affect the level of FGF23, which in turn affects phosphorus metabolism and ultimately leads to the occurrence of RLS.

In the present study, we focused on predialysis hypermagnesaemia, not serum magnesium, during a haemodialysis session. In haemodialysis patients, losing the regulatory role of the kidneys would significantly affect magnesium balance, and dialysis would be required for magnesium clearance.[24] Therefore, predialysis hypermagnesaemia might simply reflect inadequate clearance in haemodialysis. We should be very cautious in drawing conclusions about the relationship between uraemic RLS and its risk factors, including predialysis hypermagnesaemia but also dialysis duration and predialysis hyperphosphataemia, based on the present study's results.

In the clinical setting, not only hypermagnesaemia but hyperphosphataemia is common in maintenance haemodialysis patients, leading to acute or chronic problems, including haemodynamic instability, arrhythmias, cardiovascular disease and bone disease.[25–27] In vitro and animal studies have shown that higher serum magnesium concentration may have a long-term protective effect due to its inhibitory role in vascular calcification.[28] These findings, combined with our current ones on the potential effect of hypermagnesaemia on uraemic RLS, indicate it is reasonable to focus on maintaining serum magnesium concentration within the normal range by adjusting the concentration of magnesium in dialysate.

The current study had several limitations. The retrospective study design and the small sample size decreased the power of the conclusions. It was an association study about clinical phenomena without any mechanism analysis or intervention measures. As described above, predialysis hypermagnesaemia might merely reflect inadequate clearance during haemodialysis; thus, we should be careful in drawing conclusions about the relationship between uraemic RLS and its risk factors. A rational prospective randomised controlled trial should be designed to overcome these limitations.

In conclusion, we retrospectively investigated a maintenance haemodialysis patient cohort and found that predialysis hypermagnesaemia was independently associated with morbidity of uraemic RLS. Compared with patients who did not have predialysis hypermagnesaemia, those who had it experienced an increase in morbidity of uraemic RLS. Our data provide evidence that it is important to maintain magnesium stability in maintenance haemodialysis patients.

Author affiliations
[1]Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China
[2]Department of Nephrology, Jinhua Municipal Central Hospital, Jinhua, China
[3]Department of Nephrology, Beilun People's Hospital, Ningbo, China
[4]Department of Nephrology, Yiwu Municipal Central Hospital, Yiwu, China
[5]Department of Nephrology, The Fourth Affiliated Hospital, College of Medicine, Zhejiang University, Yiwu, China

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Contributors YY participated in study design and wrote the manuscript. HY, QH, XZ and BY were involved in data acquisition. YY and JY analysed the data. JC supervised the study. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Competing interests None declared.

Patient consent for publication Obtained.

Ethics approval The study was approved by the Institutional Ethics Committee of Zhejiang University, in accordance with the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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