

Impact of different stages of chronic kidney disease on the severity of Willis–Ekbom disease

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ABSTRACT

Introduction: Willis–Ekbom disease (WED)/restless legs syndrome (RLS) is a disorder in which the patient has neurologic features such as urge of rhythmic limb movement that may decrease or stop when the limb is moved. In this study, we had tried to compare the severity of WED in different stages of chronic kidney disease (CKD). **Materials and Methods:** In this study, a total of 300 patients with CKD who were >18 years of age were included. All the participants were subjected to questionnaire for the diagnosis of RLS (essential clinical criteria for the diagnosis of RLS) and a questionnaire on International Restless Legs Syndrome Study Group Rating Scale for its severity. **Observation and Results:** Our study showed a prevalence of 20% of WED in patients with CKD. Patients with CKD on hemodialysis had significantly more WED than the conservative group ($P = 0.0001$). Patients with a history of diabetes mellitus showed significant correlation with WED ($P = 0.026$), while patients who had a history of hypertension showed both diabetes mellitus and hypertension and smoking had no significant relation with WED ($P = 0.27$, $P = 0.23$, and $P = 0.22$, respectively). The different stages of CKD showed significant correlation with WED ($P = 0.002$), with more WED among patients with stage V CKD. WED was more in patients on hemodialysis ($P = 0.0001$). The correlation of different stages of CKD with the severity of WED was statistically significant ($P = 0.029$), with WED being more severe among stage V CKD. **Conclusion:** WED was more prevalent among patients with CKD who are on maintenance hemodialysis and diabetes mellitus. However, no such relation could be established for hypertension alone. Patients with higher grades of CKD were more prone to have WED symptoms, and the severity of these symptoms increases with the stages of CKD.

Keywords: Chronic kidney disease, restless legs syndrome, severity, Willis–Ekbom disease prevalence

Implications of clinical practice

- WED is a commonly occurring but a frequently underdiagnosed and neglected condition among patients with chronic kidney disease (CKD)
- This article gives an insight into why physicians must focus on symptoms of WED to improve patient care
- In this study, the correlation of WED with various stages of CKD depicts that it is more severe in advanced disease and

it increases among patients undergoing hemodialysis which is a major part of CKD management

- Hence, a physician must have a background knowledge about WED to diagnose and manage it.

Introduction

Willis–Ekbom disease (WED), also known as restless legs syndrome (RLS), is a disorder in which the patient has neurologic features such as urge of rhythmic limb movement that may decrease or stop when the limb is moved, seen in 5%–10% of the populations.^[1] Certain conditions that predispose WED include

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anemia, increasing age, female gender, rheumatoid arthritis, pregnancy, and chronic kidney disease (CKD).^[2-6] This condition produces sensations over arms and legs and sometimes over other body parts as well and this sensation is uncomfortable till the patient moves his or her limb. The patients usually complain of a creepy crawly sensation associated with itchiness and sometimes pin- and needle-like feeling.^[7,8] WED symptoms usually get aggravated on rest or simply lying down for some time. It is also associated with reduced sleep, decline in quality of life, increased cardiovascular morbidity, and increased mortality, especially in patients with CKD with a prevalence of 20%–60%.^[9-14]

In patients with CKD, WED is probably due to iron deficiency. Patients undergoing hemodialysis may further exacerbate iron deficiency, therefore worsening WED symptoms. Simultaneously, presence of anemia because of blood loss directly during dialysis, frequent investigations, and low erythropoietin also contribute to the cause.^[15,16]

No accurate pathophysiological mechanism of WED has been found yet in patients with CKD, but there have been various hypotheses that have been postulated; they are as follows:

1. Neurotransmission in the brain carried out by dopamine and the effect of iron metabolism
2. Increased WED risk and the role of PTPRD, BTBD9, TOX3, EIS1, and MAP2K5/LBXCOR1 genes
3. Role of parathyroid hormone: patients with CKD have a higher risk of decreased parathyroid hormone. Few studies show that people with WED have low parathyroid hormone level.^[2,5,6]

When the symptoms of WED are fully developed, the diagnosis is fairly straightforward. However, when WED is more subtle in presentation or presents along with nonmotor symptoms, the diagnosis is more challenging.^[3] A comprehensive understanding of expanded symptoms and also of associated comorbidities can help doctors to manage WED. There is some negative effect of WED symptoms on patients' quality of life and general health, as well as the likelihood for misdiagnosis, which makes it important for physicians to know how to recognize, investigate, diagnose, and manage WED. It is a disease that is more frequently reported in females and the risk increases in multiparous women.^[5,17] Primary WED and secondary WED are phenotypically similar and are indistinguishable on initial presentation. Primary idiopathic WED is not age-specific. There may be genetic predispositions for patients with primary WED; however, secondary WED may be triggered by medications or maybe due to any other secondary conditions such as CKD. Severe WED is a chronic condition, whereas patients with milder forms of WED exhibit a variable pattern and have long periods of remissions. Knowledge of the mild disorder is limited as patients with mild forms seldom seek for medications and advice. Almost 40% of primary WED adults have experienced some symptoms in their childhood and undergo remission even before symptoms reappear in their third to fourth decade of life.^[17,18]

Data are variable regarding the prevalence of WED in patients with CKD who are on conservative management and among the general population. These reports put a question on the contribution of CKD in the development of WED. Some articles do show WED prevalence among patients with CKD on conservative management. In this study, we have tried to find out the prevalence of WED in this part of our country as there is lack of study on literature search by PubMed, Medlar, and Scopus, and hence it remains an underdiagnosed entity.

Materials and Methods

This cross-sectional study was done among all consecutive patients diagnosed with CKD above 18 years of age in rural teaching hospital Wardha from September 2016 to September 2018 after obtaining permission from the institutional ethics committee [Reg No. DMIMS (DU)/IEC/2016-17/4074]. All patients suffering from thyroid disorders, Parkinson's disease, and peripheral neuropathy [ruled out by clinical evaluation as nerve conduction velocity (NCV) was not done due to financial constraint; deep tendon reflex examination is the cornerstone to examine neuropathies, a focal loss of deep tendon reflex; absence of ankle jerks with preserved reflex at other sites suggests length-dependent axonopathies]^[19] and patients on antipsychotics, antidepressants, anticonvulsants, statins, and steroids; and alcohol consumers were excluded from the study.

A detailed information regarding patients past medical disorders and pharmacological interventions was taken. All participants were subjected to general and systemic examination. Each patient was provided with an RLS activity questionnaire by a third person who was oblivious to the nature of the study and its possible outcome to avoid bias. The diagnosis of disease status was exclusively based on patient's medical history alone. Diseases that were considered in this study were hypertension and type II diabetes mellitus. Patients who had a history of smoking were also considered. General examination was done and vitals were checked; blood pressure was taken in right arm supine position by auscultatory method. Patients with CKD were defined as per Kidney Disease Outcomes Quality Initiative (K/DOQI) criteria, as given below:

Kidney damage for ≥ 3 months, as defined by the structural and functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR), manifested by markers of kidney damage, including abnormalities in the composition of blood or urine or abnormalities of imaging tests and $\text{GFR} < 60 \text{ mL}/\text{min}/1.73 \text{ m}^2$ for 3 months, with or without kidney damage.^[20]

Diagnosis of WED was done on the basis of essential clinical criteria for its diagnosis.^[8]

The severity of RLS was evaluated by questionnaire on International Restless Legs Syndrome Study Group Rating Scale for Severity of Restless Legs Syndrome.^[21,22]

CKD and its stages were defined by equation for modification of diet in renal disease – estimated GFR (mL/min per 1.73m²) = 186.3 × P_{cr} (e^{-1.154}) × age (e^{-0.203}) × (0.742 if female) × (1.21 if black).^[23]

Statistical analysis

Statistical analysis was done using descriptive and inferential statistics. The following test was used for this purpose: Chi-square test, Student’s unpaired *t*-test, and multiple logistic regression analysis. We used SPSS 22.0 version software for evaluation and GraphPad Prism 6.0 version. *P* value <0.05 was considered as the level of significance.

Observation and Results

In this study, we included 300 patients who had CKD; the mean age of male patients was 46.55 ± 15.38 years, the mean age of female patients was 50.58 ± 13.66 years, and the mean age of all patients was 47.58 ± 15.04 years. Of 300 patients, there were 223 (74.33%) males and 77 (25.67%) females. Of 300 patients, 115 (38.33%) patients were on conservative management and 185 (61.67%) patients were on maintenance hemodialysis (MHD). In all, 146 (48.67%) patients had a history of hypertension, 72 (24%) patients had a history of diabetes mellitus, and 139 (46.33%) patients had a history of smoking. All the baseline characteristics are shown in Table 1.

Among 300 patients, 115 (38.33%) patients were under conservative management; of these, 6 (5.22%) had WED and 109 (94.78%) did not have WED. In all, 185 (61.67%) patients were on MHD, of which 54 (29.19%) had WED and 131 (70.81%) did not have WED. Of the 300 patients included in this study, 60 (20%) had WED, whereas 240 (80%) did not have WED. The correlation of management with WED was statistically significant ($\chi^2 = 25.47, P = 0.0001$), as shown in Table 2.

Of the 300 patients in this study, 72 (24%) patients had a history of diabetes mellitus, and of these 21 (29.17%) had WED and 51 (70.83%) did not have WED. Of 300 patients, 146 (48.67%) patients had a history of hypertension, of which 33 (22.60%) had WED whereas 113 (77.40%) did not have WED. The correlation of history of hypertension with CKD with WED was statistically not significant ($\chi^2 = 1.20, P = 0.27$). In our study, 77 (25.67%) patients had both diabetes mellitus and hypertension; of these 77 patients, 19 (24.68%) had WED and 58 (75.32%) did not have WED. A total of 223 (74.33%) patients did not have diabetes mellitus nor hypertension. In all, 41 (18.39%) of these patients had WED, whereas 182 (81.61%) did not have WED. The correlation of history of diabetes mellitus along with hypertension in patients with CKD with WED was statistically not significant ($\chi^2 = 1.41, P = 0.23$). Of 300 patients, 139 (46.33%) patients had a history of smoking, of which 32 (23.02%) had WED and 107 (76.98%) did not have WED. About 161 (53.67%) patients were not smokers, of which 28 (17.39%) had WED and 133 (82.61%) did not have WED. The

Table 1: Baseline characteristics

| Variables | Number (Standard Deviation) | Percentage |
|----------------|-----------------------------|------------|
| Age (in years) | 47.58±15.04 | |
| Sex | | |
| Male | 223 | 74.33% |
| Female | 77 | 25.67% |
| Risk factors | | |
| HTN | 146 | 48.67% |
| DM | 72 | 24.00% |
| HTN + DM | 77 | 25.67% |
| Smoking | 139 | 46.33% |
| Anemia | | |
| Mild | 7 | 16.67% |
| Moderate | 20 | 33.33% |
| Severe | 33 | 55% |
| RLS | 60 | 20% |
| MHD | 185 | 61.67% |
| Conservative | 115 | 38.33% |

HTN: Hypertension; DM: Diabetes mellitus; RLS: Restless legs syndrome; MHD: Maintenance hemodialysis

Table 2: Correlation of management with RLS

| Management | RLS present | RLS absent | Total | χ^2 |
|--------------|-------------|--------------|--------------|----------------------------|
| Conservative | 6 (5.22%) | 109 (94.78%) | 115 (38.33%) | 25.47, <i>P</i> =0.0001, S |
| MHD | 54 (29.19%) | 131 (70.81%) | 185 (61.67%) | |
| Total | 60 (20%) | 240 (80%) | 300 (100%) | |

RLS: Restless legs syndrome; MHD: Maintenance hemodialysis

correlation of history of smoking with WED was statistically not significant (*P* = 0.22), as shown in Table 3.

Of 300 patients in this study, 8 (2.67%) patients had stage I CKD, of which no patient had WED. A total of 36 (12%) patients had stage II CKD, of which 2 (5.56%) had WED and 34 (94.44%) did not have WED. Totally 39 (13%) patients had stage III CKD; among them, 2 (5.13%) had WED and 37 (94.87%) did not have WED. Thirty-three (11%) patients had stage IV CKD; among them, 7 (21.21%) had WED and 26 (78.79%) did not have WED. In all, 184 (61.33%) patients had stage V CKD, of which 49 (26.63%) had WED and 135 (73.37%) did not have WED. The correlation of CKD with WED was statistically significant ($\chi^2 = 17.17, P = 0.002$), as shown in Table 4.

Discussion

In this study, we found 20% prevalence of WED in patients with CKD both on conservative management and on hemodialysis. The primary outcome of this study was to see the prevalence of WED in patients with CKD, and the secondary outcome was to see the severity of WED with increasing stage of CKD.

Various risk factors such as diabetes mellitus, hypertension, and smoking were seen as to how it contributes to the development of WED in patients with CKD. In this study, we found a significant correlation of increased incidence of WED in patients undergoing hemodialysis when compared with patients who were on conservative management. This result was similar

Table 3: Correlation of risk factors with RLS and its severity

| | RLS absent | RLS present | | | | | |
|----------|--------------|--------------|--------------|-----------|-------------|------------|-------------|
| | | Total | None | Mild | Moderate | Severe | Very severe |
| DM | 228 (76%) | 72 (24%) | 51 (70.83%) | 4 (5.56%) | 4 (5.56%) | 9 (12.50%) | 4 (5.56%) |
| HTN | 154 (51.33%) | 146 (48.67%) | 113 (77.40%) | 6 (4.11%) | 14 (9.59%) | 6 (4.11%) | 7 (4.79%) |
| HTN + DM | 223 (74.33%) | 77 (25.67%) | 60 (77.92%) | 3 (3.90%) | 3 (3.90%) | 4 (5.19%) | 7 (9.09%) |
| Smoking | 161 (53.67%) | 139 (46.33%) | 107 (76.98%) | 4 (2.88%) | 16 (11.51%) | 7 (5.04%) | 5 (3.60%) |

RLS: Restless legs syndrome; DM: Diabetes mellitus; HTN: Hypertension

Table 4: Correlation of severity of RLS with different stages of CKD

| | Stage I | Stage II | Stage III | Stage IV | Stage V | Total |
|-------------|-----------|-------------|-------------|-------------|--------------|------------|
| None | 8 (100%) | 34 (94.44%) | 37 (94.87%) | 26 (78.79%) | 135 (73.37%) | 240 (80%) |
| Mild | 0 (0%) | 1 (2.78%) | 1 (2.56%) | 1 (3.03%) | 7 (3.80%) | 10 (3.33%) |
| Moderate | 0 (0%) | 1 (2.78%) | 1 (2.56%) | 2 (6.06%) | 24 (13.04%) | 28 (9.33%) |
| Severe | 0 (0%) | 0 (0%) | 0 (0%) | 3 (9.09%) | 10 (5.43%) | 13 (4.33%) |
| Very severe | 0 (0%) | 0 (0%) | 0 (0%) | 1 (3.03%) | 8 (4.35%) | 9 (3%) |
| Total | 8 (2.97%) | 36 (12%) | 39 (13%) | 33 (11%) | 184 (61.33%) | 300 (100%) |

$$\chi^2=28.35, P=0.029, S$$

RLS: Restless legs syndrome; CKD: Chronic kidney disease

to a study conducted by Santos *et al.* and de Menezes where this significance was due to increase in serum parathormone or due to anemia (decreased hemoglobin) irrespective of iron status.^[24,25] In another study, they have attributed this to the proinflammatory nature of dialysis as a physiological basis for patients on prolonged hemodialysis.^[26]

Risk factors such as diabetes were associated with an increased prevalence of WED in patients with CKD; however, no significant correlation was found with hypertension and smoking. This increase in WED in diabetes mellitus may be due to a decrease in dopamine in striatum and midbrain as found in animal models though similar studies are lacking in humans.^[27]

In our study, we have seen an increase in WED with increasing stages of CKD. However, studies have shown lower prevalence of RLS among patients with end-stage renal disease.^[28] Also, there were studies that showed higher prevalence of RLS among CKD population.^[29] Patients with CKD stages I, II, and III were on conservative management, and in stage IV only a few patients went for hemodialysis. Patients on stage V were mostly on hemodialysis. These data are synchronous with the fact that WED is more prevalent among patients undergoing hemodialysis. This may be also because of the increased number of hemodialysis patients in our study. Few studies done earlier in patients with CKD have used the questionnaire to diagnose the WED, and this may be the reason behind the highly reported prevalence of WED. It was seen that the prevalence of WED fell to 4.5% after clinical examination and face-to-face interview compared with 21% which was a questionnaire-based approach.^[30]

Limitations

The study lacked in its analysis for serum iron studies, parathormone levels, and other laboratory parameters which could have helped determine the etiology of our observation. We ruled out peripheral neuropathy by clinical examination

alone; however, NCV test could have provided with objective evidence for the same.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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