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# RESTLESS LEGS SYNDROME IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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## ABSTRACT

**Objective:** To determine the frequency of restless legs syndrome (RLS) and its associated factors in patients with type 2 diabetes mellitus. **Design and Methods:** It was single centered, cross-sectional study done with convenient sampling. The study population comprised 174 subjects (120 diabetics and 54 non-diabetics). Participants were recruited from the Diabetes clinic of Jinnah Medical College Hospital, Karachi. The relevant clinical and laboratory parameters were obtained by clinical history and chart review. Multivariable logistic regression was done to identify the factors of RLS among diabetics. **Results:** Using the International RLS Study Group (IRLSSG) criteria, RLS was identified only in 67(55.8%) subjects from the diabetic group. The mean age of RLS subjects was 56±8 years as compared to 46±8 years in the non-RLS subjects. Forty percent (26/67) of the diabetic/RLS+ subjects had diabetes for >10 years and had significantly deranged glycemic indices. Periodic limb movements during sleep (PLMS) as reported by the bed partner or close family member were reported by 32(26.7%) of the diabetic subjects only; of which 21(65.6%) subjects had RLS. Sleep disturbances were more frequent among patients with RLS as compared to non-RLS (61.2% versus 21.5%). According to Semmes-Weinstein filament test, 61% of diabetics and 67% of diabetic/RLS subjects had peripheral neuropathy. Interestingly, none of our subjects who were diagnosed as RLS was ever asked by their physician for symptoms of RLS prior to this study. **Conclusion:** RLS is a common problem among patients with type 2 diabetes mellitus and is associated with increasing age, peripheral neuropathy and impaired day time functioning. Poor recognition by physicians result in delayed diagnosis.

**Keywords:** Restless leg syndrome (RLS), diabetes mellitus, polyneuropathy

## INTRODUCTION

Restless legs syndrome (RLS) is a chronic sensorimotor disorder [1-4]. RLS can either be primary or secondary. Primary or idiopathic RLS, diagnosed when clinical conditions responsible for secondary forms are excluded by laboratory and clinical examinations, accounts for about 70 -80% of all RLS cases [1,5]. Among secondary or symptomatic forms, several conditions such as iron deficiency anemia, uremia, pregnancy, polyneuropathy and type 2 diabetes mellitus have been implicated in association with RLS [6-11]. RLS has recently been characterized by The International Restless Legs Syndrome Study Group (IRLSSG) as a clinical syndrome presenting as a combination of intense desire to move the limbs associated with paresthesias/dysesthesias; motor restlessness; exacerbation of symptoms with inactivity and relief by activity; and a nocturnal worsening in the symptom [12]. According to the Western data, it affects approximately 7-11.5% of the adult population and is found to be higher in women than in men. The intensity of sensory and motor symptoms generally tends to increase with advancing age. Alcoholics, smokers and selective serotonin reuptake inhibitor (SSRI) users as well as patients suffering from neuropathy are more likely to have RLS [2, 13-16]. Diabetes mellitus is a lifelong disease and a common cause of sensorimotor polyneuropathy [13]. However, previous studies on RLS in diabetic neuropathy yielded conflicting results with a prevalence rate ranging from 8.8 to 27%, not significantly different even from controls in some studies [11, 17-18]. Poor glycemic control with RLS may also impact the associated consequences of diabetes mellitus including sleep quality, sleep cycle alterations, fatigue, and depression [19]. Norma G et al reported that diabetic people at risk for RLS were at increased risk for obstructive sleep apnea and insomnia-sleep problems often reported in diabetes [19]. Montplasir et al reported significant association between RLS and Periodic Limb Movements during Sleep (PLMS) during sleep or while

awake [20]. However, there is paucity of local data in this regard. We hypothesized that patients with type 2 diabetes mellitus will show a high frequency of RLS. Therefore, we sought to determine the frequency of RLS in subjects with type 2 diabetes mellitus and its associated factors especially sleep disturbances, daytime time functioning and PLMS. with non-adherence to AEDs and help in taking possible measures to improve antiepileptic drug compliance and prevent consequences of uncontrolled seizures. The prevalence of epilepsy in Pakistan is about 9.99/1000.

## METHODS

### Patient selection

For this study, 120 consecutive subjects with type 2 diabetes mellitus who attended the diabetes clinic of Jinnah Medical Dental College Hospital, Karachi from July 2009 to July 2010 were recruited. Ethical approval for the study was taken from local ethics review committee of the hospital. The non-diabetic group consisted of 54 consecutive patients who attended the medical outpatient clinics for some seasonal illness during the study period with no sign/symptom of any chronic disease. We included all the subjects who were 30 years old or above, irrespective of the gender. We excluded all the patients who were known to have (or were being treated for) anemia, chronic liver disease, thyroid dysfunction, uremia and non-diabetic polyneuropathy. Similarly, pregnant women were excluded from the study as RLS is already expected to be more prevalent in this set of population. Patients who had a language barrier were also excluded to minimize the biases in clinical findings and ensure the authenticity of information. All the participants provided an informed consent.

### General Protocol

Records were reviewed and patients were interviewed using a closed ended questionnaire regarding their demographic aspects, past medical history, family history and use of medications. In particular, we inquired about the clinical conditions which support RLS (such as iron-deficiency anemia, hypothyroidism, uremia, and rheumatoid arthritis) and about the drugs which could possibly worsen RLS symptoms (antidepressants or antipsychotics) or rather improve RLS symptoms (dopaminergic agents, benzodiazepines, and anticonvulsants such as gabapentin, carbamazepine, oxcarbazepine, and valproic acid). Moreover, both diabetic and non-diabetic subjects were specifically asked for: (1) disturbance of sleep (2) daytime sleepiness (3) daytime dysfunction; and (4) presence of PLMS. Sleep disturbance was defined as difficulty in falling asleep and awakening. Daytime sleepiness was assessed by Epworth Sleepiness Scale (ESS) which is a validated tool. A score of >10 was indicative of excessive daytime sleepiness. [13] Patients were considered to have daytime dysfunctioning when they have a subjective complain about it. Presence of PLMS as reported by the bed partner or close family member was ascertained as described in the literature i.e. periodic jerky movements causing flexion of the ankle, knee, or hip; occasionally accompanied by arousals from sleep, leading to sleep fragmentation and excessive daytime sleepiness [18].

**Table 1: Comparison of diabetic and non-diabetic subjects**

| Variables | Diabetics n (%) | Non diabetics n (%) | *p-value* |
|---|---|---|---|
| Age(in years)* | 52.7±9.2 | 43.4±6.4 | |
| **Gender** | | | 0.40 |
| Male | 62 (51.6%) | 31 (57.4%) | |
| Female | 58 (48.3%) | 23 (42.5%) | |
| **Smoking status** | | | 0.184 |
| Smoker | 28 (23.3%) | 34 (33.3%) | |
| Ex-smoker | 22 (18.3%) | 5 (9.3%) | |
| Non-smoker | 70 (58.3%) | 31 (57.4%) | |
| **Hypertension** | 70 (58.3%) | 34 (63%) | 0.56 |
| **Family history of sleep disorder** | 4 (3.3%) | 0 (0%) | 0.17 |
| **Family history of diabetes** | 78 (65%) | 6 (11.1%) | 0.00 |
| **Family history of RLS** | 15 (12.5%) | 1 (1.9%) | 0.02 |
| **Family history of neuropathy** | 6 (5%) | 1 (1.9%) | 0.32 |
| **Disturbance of sleep** | 63 (52.5%) | 1 (1.9%) | 0.00 |
| **Daytime sleepiness** | 52 (43.3%) | 1 (1.9%) | 0.00 |
| **Impaired daytime functioning due to sleep disturbance** | 47 (39.2%) | 0 (0%) | 0.00 |
| **Periodic limb movement** | 32 (26.7%) | 0 (0%) | 0.00 |
| **Palpable peripheral pulses** | 114 (95%) | 54 (100%) | 0.09 |
| **Laboratory Parameters:** | | | |
| Hemoglobin (gm/dl)* | 10.8±1.5 | 11.8±1.5 | 0.001 |
| Ferritin (ng/ml)* | 91.5±32.4 | 95.8±26.7 | 0.6 |
| Random blood sugar (mg/dl)* | 244.9±69.3 | 145.0±23.1 | 0.00 |
| Fasting blood sugar (mg/dl)* | 136.1±56.2 | 85.0±5.9 | 0.00 |
| HbA1c* (%) | 9.5±2.3 | 1.17±0.9 | 0.00 |
| Creatinine (mg/dl)* | 1.2±0.43 | 0.9±0.08 | 0.001 |

*mean values

### RLS Protocol

In all the study subjects, a neurologist confirmed the presence of RLS using the criteria defined by the International Restless Legs Syndrome Study Group (IRLSSG) [12]. Only the patients who fulfilled all 4 criteria were considered affected by RLS and were further asked about the frequency, duration and intensity of the symptoms. Presence of RLS symptoms in first-degree relatives was established in both diabetic and non-diabetic subjects.

### Laboratory Data

Laboratory data was obtained at the time of interview

for complete blood count, creatinine, random and fasting blood glucose in all subjects and for serum ferritin and glycosylated hemoglobin (HbA1c) in 79 and 152 subjects respectively.

### Evaluation of polyneuropathy

Distal sensory function was examined bilaterally using Semmes-Weinstein (SW) filaments as recommended by the World Health Organization and International Diabetes Federation for screening peripheral neuropathy in diabetic subjects [21]. The dorsal surface of the foot and the heel was tested in a random manner on 10 predetermined sites [21-22] with the filament pressed perpendicularly, for 1 second, and pressure enough to bend the filament. Patient's response was noted on the basis of yes/no option. Those patients who were able to perceive at less than 6 points were considered to have neuropathy [21].

**Table 2: Comparison of non-RLS and RLS subjects**

| Variables | RLS- | RLS+ | p-value |
|---|---|---|---|
| **Age(in years)*** | 45±8.0 | 56±8.4 | 0.00 |
| **Gender** | | | 0.191 |
| Males | 53(49.5%) | 40 (59.7%) | |
| Females | 54(50.5%) | 27(40.3%) | |
| **Smoking** | | | 0.361 |
| Non-smoker | 65 (60.7%) | 36 (53.7%) | |
| Smoker (ex or current) | 42 (39.3%) | 31 (46.3%) | |
| **Family history of diabetes** | | | 0.00 |
| No | 70 (65.4%) | 20 (29.9%) | |
| Yes | 37(34.6%) | 47(70.1%) | |
| **Family history of RLS** | | | 0.126 |
| No | 100 (93.5%) | 58 (86.6%) | |
| Yes | 7 (6.5%) | 9 (13.4%) | |
| **Family history of sleep** | | | 0.109 |
| No | 103 (96.3%) | 67 (100%) | |
| Yes | 4 (3.7%) | 0 (0%) | |
| **Family history of neuropathy** | | | 0.033 |
| No | 47(88.7%) | 67(100%) | |
| Yes | 6(11.3%) | 0(0%) | |
| **Evidence of neuropathy^** | | | 0.00 |
| No | 90(84.1%) | 22(32.8%) | |
| Yes | 17(15.9%) | 45(67.2%) | |
| **Disturbance of sleep** | | | 0.00 |
| No | 84(78.5%) | 26(38.8%) | |
| Yes | 23(21.5%) | 41(61.2%) | |
| **Daytime sleepiness** | | | 0.00 |
| No | 94(87.9%) | 27(40.3%) | |
| Yes | 13(12.1%) | 40(59.7%) | |
| **Daytime functioning** | | | 0.00 |
| Normal | 104(97.2%) | 22(32.8%) | |
| Impaired | 3(2.8%) | 45(67.2%) | |
| **Periodic Limb Movement** | | | 0.00 |
| No | 96(89.7%) | 46(68.7%) | |
| Yes | 11(10.3%) | 21(31.3%) | |
| **Laboratory Parameters** | | | |
| Hemoglobin (gm/dl)* | 11.5±1.5 | 10.8±1.4 | 0.009 |
| Ferritin (ng/ml)* | 90.3±25.2 | 95.3±39.4 | 0.498 |
| Random blood sugar (mg/dl)* | 191.0±72.3 | 230.3±64.1 | 0.00 |
| Fasting blood sugar (mg/dl)* | 108.2±48.5 | 139.4±52.9 | 0.00 |
| HbA1c* (%) | 4.9±4.5 | 9.4±2.4 | 0.00 |
| Creatinine (mg/dl)* | 1.05±0.24 | 1.2±0.50 | 0.002 |

*mean values; ^based on SW monofilament testing score = 6

### Statistical Analysis

**Sample size estimation:** A sample size of at least 175 was required to estimate the proportion of RLS among diabetics, however there is no literature available in our region assuming 10-15% prevalence in the regional population along with 80 percent power, 0.05 significance level, 5 percent bond on error, and 5% adjustment for non-response rate. As previously reported by Rozina S et al, RLS was seen in around 10% of the general population.[7] Data was entered and analyzed using Statistical Package Social Sciences (SPSS) version 19.0. Initially descriptive statistics and frequencies and proportions were generated. Continuous variables were analyzed by t– test and categorical by chi-square or Fisher exact, where appropriate. Later stepwise multivariable logistic regression was done to identify factors related with RLS among diabetics.

## RESULTS

General characteristics of the diabetic and non-diabetic subjects are presented in Table 1. Diabetic subjects were comparably elder as compared to the non-diabetic subjects. Also, there was a slight preponderance of male gender in the diabetic subjects. Presence of sleep disorders, PLMS and RLS, family history of diabetes mellitus and RLS, and higher glycemic indices were significantly frequent among diabetic subjects. Only 34% of the diabetic subjects had a value of HbA1c < 7%. Most of the patients (94%) were taking oral hypoglycemic agents, the rest were on insulin therapy. PLMS were reported by 32 (26.7%) diabetics' subjects only; of whom 21(65%) subjects had RLS. Sixty seven of the 120 subjects with type 2 diabetes mellitus (55.8%) were diagnosed as having RLS ($p < 0.05$). Among these subjects, 28/67 (41.8%) had diabetes for < 5years, 26/67 (38.8%) for >10 years, while the rest of them (13/67; 19.4%) had diabetes for 5-10 years. The laboratory parameters of RLS subjects revealed higher values for the glycemic indices including random and fasting blood sugar; and HbA1c level (Table 2). Among RLS subjects, none reported a positive family history of any sleep disorder which was in contrast to 4 (3.7%) of the non-RLS subjects. Among the subjects who did not fulfill the RLS criteria (n;53) the individual RLS like complains were evaluated. Unpleasant sensation in the legs with urge to move them was reported in 42.8%, worsening during inactivity or rest in 25.6%, relieved by activity in 18.1% while nocturnal worsening was reported by 22.4% of non- RLS subjects. Among RLS subjects, the majority of the subjects were using over-the-counter analgesics (59/67; 88%). In univariate analysis, female gender, increasing age, clinical evidence of neuropathy, disturbance of sleep, daytime sleepiness, and impaired daytime functioning appeared as predictors of presence of RLS (Table 3). However, only advancing age, impaired daytime functioning and clinical evidence of neuropathy appeared as the predictors of RLS in multivariate analysis (Table 4). The multivariable

analysis showed that having impaired daytime functioning due to sleep disorder was 47 times more associated with RLS adjusting for other covariates (adjusted Odds Ratio (OR) 47; 95% CI 10.3-217). Likewise, odds of having RLS among those with an evidence of neuropathy were 15 times more than those without neuropathy (adjusted OR= 15, 95% CI = 3.8-58). Every one year increase in age showed a 20% increase in risk of having RLS after adjusting other variables (Adjusted OR= 1.2, 95% CI = 1.1-1.3). Interestingly, despite the high prevalence reported from the subcontinent, none of the non-diabetic subject suffered from either RLS or PLMS. To our surprise, none of the subjects who were diagnosed as RLS was ever asked by their physician for symptoms or diagnosis of RLS prior to this study.

## DISCUSSION

The reported prevalence of RLS in general population by Western countries ranges between 5-15% [23] whereas data from Asian countries has reported a lower prevalence (1.5% in Japan [24], 1% in Singapore [25], 3.19% in Turkey [26]). Recently, higher prevalence rate i.e. 9.71% [27] has been reported by a Turkish study but their study population included subjects aged 40 years and above. Population based studies have found higher prevalence rates of RLS among subjects with advanced age, increased body mass index, smoking and diabetes mellitus [28,29]. Such varied differences in ranges might be due to the reason that some have heterogeneity in study design, study population and sample size. With no local data in this regard from Pakistan, this is the first Pakistani study confirming significant association between RLS and type 2 diabetes mellitus. The frequency of RLS in our diabetic subjects (55.8%) is significantly higher than compared to the international literature. Merlino et al diagnosed the RLS on the basis of International RLS Study Group criteria and reported a prevalence of 17.7% in their study population of diabetic subjects [4]. Lopes et al reported a comparatively higher frequency of RLS in 27% of the diabetic subjects [18], which is still lower than the frequency we found in our cohort. Peripheral neuropathy has been postulated to be associated with the pathogenesis of RLS. Qu S and Jensen et al have hypothesized that RLS in diabetic subjects could be due to the concurrence of decreased inhibitory dopaminergic control on the dorsal horns of the spinal gray matter [30-31] with the excitatory nociceptive inputs due to the peripheral neuropathy [32]. Various clinical studies have reported a significant association between RLS and polyneuropathy [8,33,34]. However, Skomro et al reported an insignificant association between RLS and diabetic polyneuropathy (p-value: 0.78) [11]. In our study, odds of having RLS among those with an evidence of neuropathy were 15 times more than those without neuropathy (adjusted OR= 15, 95% CI = 3.8-58). Diabetic subjects who were affected by RLS described their symptoms as an urge to move their limbs while those who had clinical evidence of neuropathy described their symptoms as pain, electric, or burning (pricking) sensations. This is in accordance with previous results shown by Winkelmann et al and Merlino et al [4, 35] A part from neuropathy, iron deficiency anemia is a well known contributor towards symptomatic form of RLS.[10] Our iron studies have shown insignificant association between RLS/diabetic+ subjects and iron studies which was in accordance with results demonstrated by previous studies [4, 11] thus further pointing towards a lack of association. However, more clinic-pathological studies are needed to further verify this hypothesis. Significant number of RLS patients in our study reported sleep disturbance with daytime sleepiness and impaired daytime functioning which was consistent with results from previous studies on diabetic subjects. We found sleep disturbance to be associated with polyneuropathy and RLS. Similar correlation has been demonstrated by previous other studies [11, 14, 36-37]. Our study has shown a significant association between RLS and PLMS as the majority of the PLMS patients were suffering from RLS too. In addition to diabetes, studies have also reported a significant association of RLS with diseases such as hypertension which could be due to concomitant sleep disturbances in such patients [38-41]. Advancing age and polyneuropathy have been shown to be associated with an increased prevalence of RLS [18,28]. The multivariate analysis established this association in our subjects as well (Table 2). A large number of our non-RLS subjects were those who suffered from a combination of symptoms included in the IRLSSG diagnostic criteria but they however, failed to meet all 4 criteria to be defined as RLS. We assume that these patients might be a potential case of RLS and may be defined as possible or probable RLS later. We propose that this criterion might be revised to take into account these large number of potential RLS patients so that early diagnosis and thus early identification of risk factors and their treatment might help them to enjoy a better quality of life. Interestingly, none of the non-diabetic subject suffered from either RLS or PLMS. Most importantly, none of our RLS subjects were ever asked by their physician for symptoms or diagnosis of RLS prior to this study. This may be because of the poor awareness of RLS among physicians as well.

## LIMITATIONS

Our study was a single centered study so results cannot be generalized over the whole population. Ideally the

patients who are suspected to have neuropathy by SW monofilament testing should undergo a standard nerve conduction study –the gold standard for the confirmation of neuropathy. Also, PLMS needs to be diagnosed with standard polysomnography.

**Table 3: Univariate logistic regression along with 95% CI for predicting factors associated with RLS among diabetics**

| Predictors | RLS - | RLS + | OR | (95% CI) | *p-value* |
|---|---|---|---|---|---|
| **Age** | 48± 8.6 | 56±8.3 | 1.1 | 1.05-1.2 | 0.00 |
| **Gender** | | | | | |
| Mates | 22(35.5) | 40(64.5) | 1 | | |
| Females | 31(53.4) | 27(46.6) | 0.47 | 0.2-0.9 | 0.04 |
| **Smoking** | | | | | |
| Smoker (ex- or current) | 34(64.2) | 36(53.7) | 1 | | |
| Non-smoker | 19(35.8) | 31(46.3) | 1.5 | 0.7-3.2 | 0.25 |
| **Family history of diabetes** | | | | | |
| No | 22(41.5) | 20(29.9) | 1 | | |
| Yes | 31(58.5) | 47(70) | 1.6 | 0.7-3.5 | 0.18 |
| **Family history of RLS** | | | | | |
| No | 47(88.7) | 58(86.6) | 1 | | |
| Yes | 6(11.3) | 9(13.4) | 1.2 | 0.4-3.6 | 0.7 |
| **Evidence of neuropathy*** | | | | | |
| No | 36(67.9) | 22(32.8) | 1 | | |
| Yes | 17(32.1) | 45(67.2) | 4.3 | 2.0-9.3 | 0.00 |
| **Disturbance of sleep** | | | | | |
| No | 31(58.5) | 26(38.8) | 1 | | |
| Yes | 22(41.5) | 41(61.2) | 2.2 | 1.06-4.6 | 0.03 |
| **Daytime sleepiness** | | | | | |
| No | 41(77.4) | 27(40.3) | 1 | | |
| Yes | 12(22.6) | 40(59.7) | 5.06 | 2.2-11.3 | 0.00 |
| **Daytime functioning due to sleep disturbances** | | | | | |
| Normal | 50(94.3) | 22(32.8) | 1 | | |
| Impaired | 3(5.7) | 45(67.2) | 34.0 | 9.5-121.6 | 0.00 |
| **PLMS** | | | | | |
| No | 42(79.2) | 46(68.7) | 1 | | |
| Yes | 11(20.8) | 21(31.3) | 1.7 | 0.7-4.0 | 0.19 |
| **Laboratory Parameters** | | | | | |
| Hemoglobin (gm dl) | 11.5±1.4 | 10.8±1.42 | 0.87 | 0.6-1.1 | 0.32 |
| Ferritin (ng ml) | 90.3±24.6 | 95.2±39.4 | 1.007 | 0.9-1.0 | 0.3 |
| Random blood sugar (mg dl) | 191.0±75.4 | 250.5±64.1 | 1.003 | 0.9-1.0 | 0.3 |
| Fasting blood sugar (mg dl) | 108.2±60.3 | 139.4±52.9 | 1.002 | 0.9-1.0 | 0.4 |
| HbA1c (%) | 9.7±2.2 | 9.4±2.4 | 0.9 | 0.7-1.1 | 0.4 |
| Creatinine (mg dl) | 1.0±0.3 | 1.2±0.5 | 1.8 | 0.7-4.5 | 0.18 |

*Mean values; ^based on SW monofilament testing score ≤ 6

## STRENGTHS

This will be the first study from Pakistan which has addressed the frequency of RLS and its association with diabetes mellitus. Therefore, the results of this study are important as they provide the insight into this important and potentially treatable medical disorder in the local perspective. In addition to results shown above, our study has also shown the utility of SW monofilament in screening for the presence of sensory neuropathy. This is important in view of World Health Organization (WHO) report which has stated that 32% of the Pakistani population lives below poverty line.

**Table 4: Multivariable logistic regression along with 95% CI for predicting factors associated with RLS among diabetics**

| Variable | ORs | 95% CI | *p-value* |
|---|---|---|---|
| **Age** | 1.2 | 1.1-1.3 | <0.00 |
| **Impaired daytime functioning due to sleep disorder** | | | |
| No | 1 | | |
| Yes | 47.3 | 10.3-217 | <0.00 |
| **Evidence of neuropathy** | | | |
| No | 1 | | |
| Yes | 15.1 | 3.8-58 | <0.00 |

Hence, nerve conduction study (NCS/EMG) is not an economically pliable tool for the diagnosis of sensory neuropathy in our general community. So, SW filament utility has again come up in our study as a useful tool.

## CONCLUSION

RLS is a common problem among patients with type 2 diabetes mellitus and is associated with increasing age, peripheral neuropathy and impaired day time functioning. Its diagnosis is often delayed because of poor recognition by the physicians. Early diagnosis may result in improved quality of life of these patients. Considering a substantial number of subjects with one or more symptoms suggestive of RLS in the non-RLS group, further studies with larger sample size are needed to establish the importance of individual symptoms to guide the investigation and the therapy in this sub-set of patients.

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