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Sleep Medicine 101 (2023) 238–243

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

The prevalence and associated factors of seasonal exacerbation of subjective symptoms in Japanese patients with restless legs syndrome

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ARTICLE INFO

Article history:
Received 18 August 2022
Received in revised form
31 October 2022
Accepted 14 November 2022
Available online 15 November 2022

Keywords:
International restless legs syndrome rating scale
Reproducibility
Restless legs syndrome
Risk factor
Seasonal exacerbation

ABSTRACT

Objectives: To elucidate the prevalence of seasonal exacerbation in patients with restless legs syndrome (RLS) and identify its associated factors.
Methods: We investigated the presence/absence of seasonal exacerbation of RLS by distributing self-administered questionnaires with an interval of three years. Patients who reported having seasonal exacerbation in both surveys were defined as having seasonal exacerbation. RLS severity was determined using the International Restless Legs Syndrome Rating Scale (IRLS).
Results: Among 180 patients, 89 reported having seasonal exacerbation in the first survey. Among them, only two reported not having seasonal exacerbation in the second survey; thus, 87 (48.3%) patients were considered to have a seasonal exacerbation. Although many of them (68 out of 87, 78.2%) experienced exacerbation in spring or summer, 19 out of 87 (21.8%) reported that their symptoms worsened in fall or winter. All the patients in this study had mild to moderate degrees of RLS severity according to the IRLS score. Multiple logistic regression analyses revealed that having a family history of RLS ($p < 0.05$) and moderate RLS ($p < 0.001$) were significantly associated with the presence of seasonal exacerbation.
Conclusions: This study revealed that approximately half of all RLS patients had seasonal exacerbation of the symptoms and that about 80% of the exacerbation was observed during the spring/summer season. Moreover, seasonal exacerbation is likely to be present even in patients whose symptoms had been improved to moderate severity with pharmacological treatment.

1. Introduction

Restless legs syndrome (RLS) is a common neurological sleep disorder characterized by an irresistible urge to move ones' limbs, mainly the lower extremities, and is associated with uncomfortable or odd sensations. The symptoms typically occur at rest, being relieved by movements, and worsen mainly at night [1]. RLS often causes disturbances in sleep initiation and/or maintenance, which can result in daytime functional impairment [2].

Recently, a seasonal exacerbation of RLS symptoms has been indicated [3–5]. A study regarding internet searches in Western countries showed that the number of keyword searches of RLS was higher in summer compared to that in winter [3]. Regarding the clinical population, RLS severity was reported to be higher in summer than in winter [4]. Furthermore, a report from China showed that 34.5% of patients with RLS had seasonal variations; 15.3% had exacerbations in summer and 9.7% in winter [5].

Abbreviations: AUC, area under curve; CI, confidence interval; IRLS, International Restless Legs Syndrome rating scale; LR, likelihood ratio; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; RLS, restless legs syndrome; ROC, receiver operating characteristic; SD, standard deviation.

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https://doi.org/10.1016/j.sleep.2022.11.017
1389-9457/

However, all of these studies had a cross-sectional or retrospective design, and none of them confirmed the reproducibility of seasonal exacerbation. To determine the accurate prevalence of seasonal exacerbation of RLS symptoms in Japanese patients with RLS and to confirm the reproducibility, we used a two-point survey to ascertain the presence/absence of this phenomenon. Thereafter, we investigated the background factors of seasonal exacerbation and discussed the mechanisms of this phenomenon.

2. Methods

This study was approved by the Research Ethics Review Committee of the Institute of Neuropsychiatry and was conducted after obtaining written informed consent from all eligible participants.

A total of 226 consecutive patients who received treatment for RLS at the Yoyogi Sleep Disorder Center (Tokyo, Japan) between December 2016 and May 2017 and met the following criteria were eligible for the study: (a) Patients with RLS >20 years of age with a diagnosis of the disorder based on the International Classification of Sleep Disorders, Third Edition [6], and (b) patients who had been regularly visiting the clinic for >1 year with the purpose of receiving treatment for RLS and had been administered a fixed dosage of medication for >6 months. Patients with secondary RLS due to disorders such as neurological diseases and chronic renal diseases were not targeted. Considering the influence of chronic iron deficiency on RLS symptoms [7,8], prior to enrollment in the study, patients who had serum ferritin levels of <50 μg/L at the time of their first visit were treated with iron supplementation until they achieved ferritin levels of ≥50 μg/L. We confirmed that none of the patients with RLS developed augmentation during the study period according to the augmentation criteria created by Garcia-Borreguero et al. [9].

To assess the presence of seasonal exacerbation and the season in which RLS symptoms become most prominent, patients who met the above criteria were asked to complete a self-administered questionnaire regarding this issue. Subjects who answered "yes" to the question "Do you experience any particular seasons when the discomfort sensation becomes worse?" were defined as having seasonal exacerbation. In accordance with the answer to the additional question "When is the season for worsening?", we classified them into the groups with possible spring/summer or fall/winter exacerbations. The questionnaire was administered during two periods (between December 2016 and May 2017 and between April 2019 and March 2020) so that we could confirm the presence/absence of seasonal exacerbation. Patients with symptom exacerbation in the same season both in the 2016–2017 survey and in the 2019–2020 survey were defined as patients with definite seasonal exacerbation, while the others who reported not having the exacerbation in at least one survey were defined as patients without seasonal exacerbation. RLS severity was assessed during the survey using the International Restless Legs Syndrome scale (IRLS) [10]. In patients with seasonal exacerbation, IRLS was assessed twice between April 2019 and March 2020 during the following time points: 1) at 3 months before the expected peak period of seasonal exacerbation, and 2) at the peak period of symptomatic exacerbation; the former was defined as the baseline IRLS score during the study period, and the latter as the IRLS score at the worst season. In patients without seasonal exacerbation, IRLS was assessed only once in April 2019, under the assumption that symptoms remained stable throughout the year (Fig. 1). The following clinical descriptive variables were obtained from the patients' medical records: age at the first survey, duration of RLS morbidity, sex, presence/absence of self-reported family history of RLS, and medications for RLS both at the time of the first and the second survey.

For patients with seasonal exacerbation, in the second survey we measured the IRLS score at two points; three months before the expected seasonal exacerbation and at the time of the seasonal exacerbation, defined as "baseline IRLS score" and "IRLS score at the worst season," respectively. For patients without seasonal exacerbation, IRLS in April 2019 was determined as the "baseline IRLS score."

Demographic variables (age at the first survey and sex), duration of RLS morbidity, presence/absence of family history of RLS, and baseline IRLS scores during the study period were compared between the groups with and without seasonal exacerbation using chi-square tests for categorical variables or Mann-Whitney's *U* test for continuous variables. Factors associated with seasonal exacerbation were investigated using a series of logistic regression analyses with independent variables including age at the first survey, duration of disease morbidity, sex, presence/absence of family history, and baseline IRLS score during the study period. All variables were investigated initially in univariate models, following which we performed multivariate logistic regression analyses for all variables that showed significant associations in the univariate analysis to control for confounding factors and to determine the main correlates. For the logistic regression analyses, IRLS scores were categorized into 10 or less (mild), 11–20 (moderate), 21–30 (severe), and 31 or more (very severe) [10]. We also compared variables (age at the first survey, duration of RLS morbidity, sex, presence/absence of family history, baseline IRLS score during the study period, and IRLS score at the worst season) between the group with symptom exacerbation in spring/summer and the group with symptom exacerbation in fall/winter using the chi-square test or Mann-Whitney's *U* test.

SPSS software (version 26.0; SPSS Japan, Inc., Tokyo, Japan) was used for all the analyses, and P values < 0.05 were considered to indicate statistical significance.

3. Results

Among 226 eligible patients, 46 cases were excluded due to withdrawal of consent (n = 2) and a lack of response regarding the first (n = 34) and the second survey (n = 10). Finally, 180 cases were included in the subsequent analyses. Among these cases, 106 (58.9%) were female and the mean age (standard deviation) was 64.3 (14.5). Medications for the treatment of RLS in the patients at the first survey were as follows: dopamine agonists in 90 cases (50.0%), α2δ ligands in six cases (3.3%), benzodiazepines in eight cases (4.4%), iron preparations in two cases (1.1%), combination of two or more of the following—dopamine agonists, α2δ ligands, benzodiazepines, iron preparations, tramadol, and carbamazepine—in 72 cases (40.0%), and no medications in two cases (1.1%). Of the 64 patients with ferritin levels <50 μg/L at the first visit, 16 were still taking iron preparations at the second survey considering the possibility of the recurrent decrease in serum ferritin levels. At the second survey, medications for RLS were changed in 25 cases: dose increase in fifteen cases, decrease in two cases, and switch to other drugs in eight cases. Among them, 14 cases still had seasonal exacerbations, while the remaining 11 cases did not have seasonal exacerbation at both surveys. None of the patients had a baseline IRLS score of >20; the baseline RLS severity was mild in 120 cases and moderate in 60 cases. Among the 180 cases analyzed, 89 reported having seasonal exacerbation in the first survey. In the second survey, two out of 89 patients did not show seasonal exacerbation, and were therefore included in the group without seasonal exacerbation. Finally, 87 (48.3%) patients were considered to have seasonal exacerbation (Table 1). Most of the participants with seasonal exacerbation (85 out of 87, 97.7%) had an increase of ≥3 points in their IRLS scores [11]. Of the 87 patients with seasonal

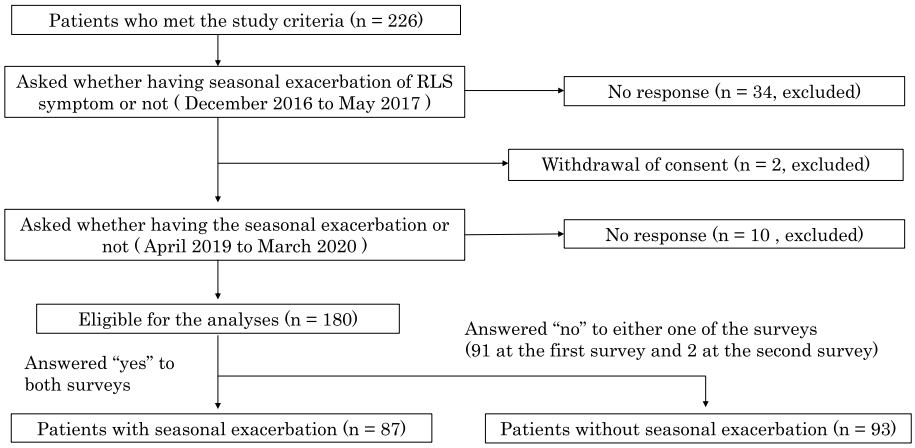

Fig. 1. Flow diagram of the survey process.

Table 1
Demographic and clinical data of patients with restless legs syndrome.

	Total (n = 180)	With seasonal exacerbation (n = 87)	Without seasonal exacerbation (n = 93)	P[a]
Age at the first survey, median (range), year	64.34 (27–93)	63.80 (28–93)	64.84 (27–88)	0.343
Duration of disease morbidity, median (range), year[b]	18.83 (0–75)	18.81 (0–75)	18.85 (2–72)	0.192
Female, n (%)	106 (58.9)	58 (66.7)	48 (51.6)	0.040*
Family history of RLS, n (%)	32 (17.8)	23 (26.4)	9 (9.7)	0.003*
RLS Medication				
Dopamine agonist, n (%)	90 (50.0)	40 (46.0)	50 (53.8)	0.296
α2δ ligands, n (%)	6 (3.3)	3 (3.4)	3 (3.2)	0.934
Benzodiazepine, n (%)	8 (4.4)	5 (5.7)	3 (3.2)	0.412
Iron preparations, n (%)	2 (1.1)	1 (1.1)	1 (1.1)	0.962
Combination, n (%)	72 (40.0)	37 (42.5)	35 (37.6)	0.503
No medications, n (%)	2 (1.1)	1 (1.1)	1 (1.1)	0.962
Baseline IRLS score, median (range), point[c]	9.58 (0–20)	11.59 (5–20)	7.70 (0–16)	<0.001*
Mild (1–10)	120 (66.7)	31 (35.6)	89 (95.7)	
Moderate (11–20)	60 (33.3)	56 (64.4)	4 (4.3)	<0.001*
Severe (21–30)	0	–	–	
Very severe (31–40)	0	–	–	
IRLS score at the worst season, median (range), point	–	16.57 (9–25)	–	–

IRLS = International Restless Legs Syndrome Rating Scale. RLS = restless legs syndrome.
*p < 0.05.
[a] Chi-square test (categorial variables) or Mann-Whitney's U test (continuous variables).
[b] Listwise deletion was utilized for 14 cases with missing data for disease onset.
[c] Confirmed at the patients' birth-month of the year (patients without seasonal exacerbation) or confirmed in non-exacerbated seasons (patients with seasonal exacerbation).

exacerbation, 68 (78.2%) reported that their symptoms worsened in spring or summer and 19 (21.8%) reported that their symptoms worsened in fall or winter.

We compared clinical descriptive variables between the patients with seasonal exacerbation and those without seasonal exacerbation. The group with seasonal exacerbation had a significantly larger proportion of females ($p < 0.05$), a larger number of individuals with a family history of RLS ($p < 0.01$), and higher baseline IRLS scores during the study period ($p < 0.001$).

In the univariate analysis, female sex (odds ratio [OR] = 1.875, 95% confidence interval [CI] = 1.026–3.428, $p < 0.05$), family history of RLS (OR = 3.354, 95% CI = 1.453–7.742, $p < 0.01$), and moderate RLS symptoms (IRLS; 11–20, OR = 40.194, 95% CI = 13.47–119.98, $p < 0.001$) were significantly associated with the presence of seasonal exacerbation. In the multiple logistic regression model, positivity for family history (OR = 3.505, 95% CI = 1.249–9.834, $p < 0.05$) and moderate RLS symptoms (OR = 42.880, 95% CI = 13.896–132.307, $p < 0.001$) were significantly associated with seasonal exacerbation (Table 2).

When comparing clinical descriptive variables between the groups with different worsening seasons, IRLS score at the worst period was significantly higher in the group with symptom exacerbation in spring/summer than in that with symptom exacerbation in fall/winter ($p = 0.010$). Other variables such as age at the first survey, duration of RLS morbidity, sex, positivity/negativity of family history, and baseline IRLS score during the study period did not show any statistical differences between these two groups (Table 3).

4. Discussion

In this study, we examined the longitudinal change in the prevalence rate of seasonal RLS symptom exacerbation and confirmed the high consistency between the two surveys conducted with an interval of three years. In contrast to previous reports, we investigated outpatients who received regular treatment for RLS. Approximately half of them had seasonal exacerbation of symptoms. Surprisingly, only two patients answered that they had seasonal exacerbations in the first survey but not in the second survey, indicating that seasonal exacerbations of RLS symptoms is highly reproducible through the course of long-term treatment. Moreover, approximately 80% of the patients with seasonal

Table 2
Factors associated with seasonal exacerbation.

	n	Univariate Relative Risk (95%CI)[a]	p	Multivariate Relative Risk (95%CI)[a]	p
Age at the first survey (years)			n.s.		
Duration of disease morbidity (years)[b]			n.s.		
Sex					
Male	74				
Female	106	1.875 (1.026–3.428)	0.041		n.s.
Family history of restless legs syndrome					
No	148				
Yes	32	3.354 (1.453–7.742)	0.005	3.505 (1.249–9.834)	0.017
Dopaminergic medication use					
No	26				
Yes	154	0.772 (0.336–1.778)	0.544		
Baseline IRLS score[c]					
Mild (1–10)	120				
Moderate (11–20)	60	40.194 (13.47–119.98)	<0.001	42.88 (13.896–132.307)	<0.001
Severe (21–30)	0	–		–	
Very severe (31–40)	0	–		–	

CI = Confidence Interval, IRLS = International Restless Legs Syndrome Rating Scale.
[a] Relative risks approximated to odds ratios.
[b] Listwise deletion was utilized for 14 cases with missing data for disease onset.
[c] Confirmed at the patients' birth-month of the year (patients without seasonal exacerbation) or confirmed in non-exacerbated seasons (patients with seasonal exacerbation).

Table 3
Comparison of the demographic and clinical data by season of exacerbation among patients with seasonal exacerbation of RLS.

	Worst during the spring/summer (n = 68)	Worst during the autumn/winter (n = 19)	p[a]
Age at the first survey, mean ± SD, years	63.78 ± 14.27	63.89 ± 13.95	0.877
Duration of disease morbidity, mean ± SD, years[b]	18.18 ± 14.79	17.11 ± 8.91	0.576
Female, n (%)	42 (61.8)	16 (84.2)	0.067
Family history of RLS, n (%)	18 (26.5)	5 (26.3)	0.989
Baseline IRLS score during the study period[c], mean ± SD	11.90 ± 2.95	10.47 ± 2.61	0.073
IRLS score at the worst season, mean ± SD	17.06 ± 3.38	14.84 ± 2.54	0.010*

RLS = restless legs syndrome, SD = standard deviation, IRLS = International Restless Legs Syndrome Rating Scale.
*p < 0.05.
[a] Chi-square test (categorial variables) or Mann-Whitney's *U* test (continuous variables).
[b] Listwise deletion was utilized for seven cases with missing data for disease onset.
[c] Confirmed at the patients' birth-month of the year (patients without seasonal exacerbation) or confirmed in non-exacerbated seasons (patients with seasonal exacerbation).

exacerbation in the present study reported that their symptoms worsened during spring and summer (warmer months), whereas the remaining patients reported that their symptoms worsened during fall and winter (colder months).

In this study, the presence of seasonal exacerbation was independently associated with a higher baseline IRLS score. In contrast to this finding, a study conducted in China found no significant differences in IRLS scores between three groups, namely summer exacerbations, winter exacerbations, and no seasonal variation [5]. However, it must be considered that the mean baseline IRLS score of the patients in this study was lower than that of the study conducted in China. Interestingly, although our study suggested that patients with a higher baseline IRLS score were more likely to have the seasonal exacerbation, the prevalence of patients with seasonal exacerbation in this study was higher than that in the abovementioned study [5]. In our study, RLS symptoms of all the patients except for two cases were pharmacologically treated and improved to a mild or moderate level, while the previous study from China included approximately equal numbers of untreated and treated patients. Further, in a study conducted in Innsbruck and Rome, summer symptom exacerbations were more pronounced in the pharmacologically treated group than in the untreated group [4]. However, it should be noted that the participants in that study had lower baseline IRLS scores in the untreated group than those in the treated group [4]. The proportion of seasonal exacerbations in patients who changed medications between the two surveys was similar to the proportion in the overall participants; the change in medications may have less of a relationship to the occurrence of seasonal exacerbations. Altogether, the abovementioned findings, indicate that patients with moderate severity of RLS symptom, are likely to experience seasonal exacerbation, even with treatment.

Another finding in the current study that is consistent with the previous report [5] was the significant association between a family history of RLS and the presence of seasonal exacerbation. Regarding patients with familial RLS, genetic mutations of neuronal nitric oxide synthase have been reported to be involved [12]. It is unclear whether there is a genetic factor in the seasonal exacerbation of RLS; however, these genetic mutations can inhibit the vasodilating effect of nitric oxide, which can cause unpleasant sensations resulting from the inability to release heat in high-temperature environments. If this is the case, patients with RLS with a family history may be more likely to have symptomatic fluctuations depending on changes in temperature. Meanwhile, onset age and duration of RLS morbidity, both of which were also associated with the presence of seasonal exacerbation in the study from China [5], did not appear as significantly associated factors in the present study. The reason for this discrepancy is unclear, but this phenomenon might be partially explained by the participants' relatively higher onset age of RLS in this study in comparison with that in the Chinese study (46.1 ± 18.7 *vs.* 38.0 ± 15.3, respectively).

The trend for exacerbation during the warm/hot season is consistent with the results of studies from Western countries and

China [3–5]. The study conducted in Rome and Innsbruck showed that the IRLS score worsened more during summer in Rome than in Innsbruck, which was explained by more pronounced seasonal temperature fluctuations in the former than in the latter city [4]. The present study was conducted in Tokyo, which has an annual temperature variation close to that in Rome. It has been speculated that iron loss from the body through perspiration may comprise one possible mechanism for the exacerbation of RLS symptoms during the warm/hot season [13]. Even though we confirmed ferritin levels of ≥50 μg/L in the participants before enrollment in this study, they possibly lost iron during summer due to heavier sweating. It has also been reported that there is no difference in the body surface temperature between patients with RLS and normal participants in normal or low temperature environments; however, in high temperature environments, patients with RLS have higher body surface temperatures than normal participants, possibly due to their impaired peripheral circulation [14]. In line with this, there have been some reports showing that cooling the body can reduce the appearance of RLS symptoms [15–17], which supports the idea that high temperature environments contribute to the occurrence of symptomatic exacerbation. Contrastingly, some reports have demonstrated that a certain degree of warmth (40–45 °C) can reduce symptoms [17,18], suggesting that individual differences may exist with regard to the effects of temperature. In the present study, a small but significant number of patients had exacerbations during winter, which is consistent with the study from China [5]. During winter, daylight hours are shorter, and this may lead to lower vitamin D levels in the blood [19]. Some studies have already demonstrated low vitamin D levels in patients with RLS [20–22]. Given that vitamin D has a protective effect on dopaminergic neurons against glutamate or other toxins [23], lower vitamin D levels may contribute to the exacerbation of RLS symptoms during the cold season. However, considering that the IRLS score at the worst season was higher in patients with spring/summer exacerbation than in those with autumn/winter exacerbation and that symptom exacerbation was more common in the hot season than in the cold season, it can be concluded that RLS symptoms may be more sensitive to heat-related bodily dynamic changes such as perspiration and temperature.

This study has several limitations. First, we only evaluated ferritin levels before the first survey and not before the second survey. Confirmation of iron status during symptom exacerbation, especially in summer, would be warranted in future studies. Second, the rate of positivity for a family history of RLS in Asian populations has been reported to range between 18 and 35% [5,24,25], which is lower than that in Caucasian populations [26]; 16% of the positivity rate in our Japanese sample could coincide with the low hereditability of the disorder in Asia. However, since the study was conducted at a single sleep disorder center, we cannot rule out the possibility that patients were not representative of the Japanese RLS population. Third, no patients with severe or very severe symptoms were included in this study; this is probably because only patients whose medication regimes remained unchanged over a six-month period were included. Thus, seasonal exacerbation of symptoms in patients with severe to very-severe RLS symptoms could not be investigated in this study. Future studies should investigate this, making adjustments for treatment drugs. Fourth, considering the possibility that depressive symptoms may affect RLS symptoms [27], the influence of seasonal change in depressive symptoms should have been evaluated. Finally, because the patients who answered not to have a seasonal exacerbation of symptoms underwent the evaluation of IRLS scores only once throughout the year at the 2019–2020 survey, the seasonal exacerbation might have been underestimated. In future studies, a seasonal assessment of symptom severity throughout the year, regardless of the presence or absence of seasonal exacerbations, may be an option for the study method. However, our methods in this study with identification of the season of symptom exacerbation in the first survey and evaluation of IRLS just prior to the symptom exacerbation and at the peak of worsening in the second survey, is also appropriate, considering that they can subjectively estimate the change in their symptom severity.

In conclusion, this study revealed that approximately half of the Japanese patients with RLS experienced seasonal exacerbation, and that a majority of them showed this phenomenon in the spring/summer, as reported previously. Notably, the seasonal exacerbation was found to be highly reproducible, and patients with moderate RLS severity and those with a family history of RLS were more likely to experience it. Furthermore, the prevalence rate as well as the degree of exacerbation was higher during the hot season. Future prospective studies should clarify the mechanism of the seasonal exacerbation and establish optimal strategies for preventing the occurrence of this phenomenon.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Moeko Sato: Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization. **Kentaro Matsui:** Conceptualization, Methodology, Validation, Writing – review & editing. **Taeko Sasai-Sakuma:** Conceptualization, Supervision. **Katsuji Nishimura:** Funding acquisition, Supervision. **Yuichi Inoue:** Conceptualization, Methodology, Resources, Writing – review & editing, Project administration.

Declaration of competing interest

None

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.

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