

Sleep Abnormalities in Guillain Barre Syndrome: A Clinical and Polysomnographic Study

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Abstract

Purpose: We analyzed the polysomnographic (PSG) profile and various factors contributing to sleep disturbances in patients with GB Syndrome.

Methodology: This prospective hospital based study included 30 adults with GB syndrome (mean: 34.30 \pm 1.40 years; M:F=24:6). All patients underwent evaluation with phenotypic details, nerve conduction studies, sleep questionnaires and over-night polysomnography (PSG). Three (10%) patients had baseline sleep disturbances with a Pittsburgh Sleep Quality Index (PSQI) of >5 and all the 3 patients continued to have poor sleep during hospitalization. Sixteen (53.3%) patients had poor sleep during their hospital stay as assessed by Richards score. Sleep disturbances as per St Mary's sleep score depicted similar observations over 10 nights. Overnight PSG was carried out within 1st to 12 day of hospitalization (mean: 6.83 \pm 3.07; median: 6.5).

Results: During overnight PSG several patients did not have all the stages of sleep: stage 1-2 patients, stage 3-6 patients, stage 4-13 patients and REM stage -7 patients. Other notable PSG observations were: increased stage 1 and stage 2 sleep, reduced stage 4 and REM sleep, decreased sleep efficiency of $<85\%$ -28; increased sleep onset latency of >30 min -4; duration of sleep of <6 hours -20; and increased arousal (arousals >5 /hour) -6. Majority of arousals were due to respiratory events and oxygen desaturation. Three patients had abnormal periodic leg movement (PLM) arousal index (>5 /hours). Sub-analysis revealed that depressed patients had lesser duration of sleep ($p=0.049$). There no REM related behavioral disorder noted.

Conclusions: To conclude, sleep disturbances and altered sleep architecture in GB syndrome during hospitalization are common and may be multifactorial.

Keywords: Guillain barre syndrome; Polysomnography; Sleep disturbances

Introduction

Sleep is an important predictor of quality of life and has been the subject of current research in many systemic and neurological disorders. Similar to the disorders of Central Nervous System (CNS), sleep disturbances have also been studied in a few disorders of Peripheral Nervous System (PNS) like diabetic neuropathy, myotonic dystrophy, and myasthenia gravis. Sleep disturbances in these disorders are ascribed to sensory phenomenon, respiratory events and mental burden of the disease e.g. pain and depression in diabetic neuropathy [1], restless leg syndrome in alcohol induced neuropathy [2] and multifocal motor neuropathies [3], respiratory muscle weakness and sleep disordered breathing in neuromuscular disorders like amyotrophic lateral sclerosis [4], and myasthenia gravis [5]. In myotonic dystrophy, excessive day time sleepiness is postulated to be due to defect in central dysregulation of sleep rather than sleep apnea [6].

Patients with Guillain Barre syndrome (GBS) experience sensory disturbances including pain, motor disability, require prolonged hospital stay and exhibit anxiety regarding uncertain nature of the disease and may be expected to have sleep disturbances. Cohen et al. in their study involving patients of GBS, admitted in ICU setup, had shown REM behavioral disorders, REM onset sleep, REM with atonia and abnormal eye movements in NREM sleep [7]. From this center, Karkare et al. had noted both quantitative and qualitative sleep disturbances in a cohort of 60 patients with GB syndrome [8]. The sleep disturbances were possibly due to anxiety, pain, paresthesia, and severity of immobility and it improved after the 1st week of inpatient care.

We analyzed the polysomnographic (PSG) profile in patients with GB syndrome and studied various factors contributing to sleep disturbances.

Patients and Methods

This prospective hospital based study involved 30 patients with GB syndrome (mean: 34.3 \pm 1.4 years; median: 31; M:F=24:6) evaluated at the Department of Neurology of a tertiary care university hospital (NIMHANS, Bangalore, India). The diagnosis was based on the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) criteria for GB syndrome [9]. Ethical approval was obtained from the Institutional ethics committee. Informed consent was obtained from the patient and/or care giver. Patients with respiratory distress, who didn't consent, or who were evaluated within 48 hours of admission were excluded. Respiratory distress in patients with GB syndrome was detected with standard bedside clinical methods like single breath count, respiratory rate, laboured breathing, use of accessory muscle, paradoxical breathing, and sometimes low

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oxygen saturation and impaired blood gas reports. Information was noted on a predesigned digital data sheet. The study was divided into following parts:

Clinical evaluation and laboratory tests

Information regarding the demographic characters, duration and severity of illness, presence of paresthesia, pain, weakness and their duration, and antecedent event was obtained. Details of blood pressure, single breath count, chest expansion and routine neurological examination were recorded. Pain and paresthesia were measured using Wong and Baker Face scale [10]. Patients were explained about the scale and were required to give a score separately for pain and paresthesia. Verbal rating scale was also used with 0 as having no pain and 10 reflecting most severe pain [11]. Severity of GBS was assessed using Hughes severity score [12], Modified Rankin score [13]. Anxiety and depression were measured using hospital anxiety and depression scale (HADS) [14]. Investigations included: hemogram, serum biochemistry including creatine phosphokinase (CPK), potassium, RA, ANA, HBsAg and HIV; Urine for porphobilinogen and Bence Jones protein; and CSF analysis. All patients underwent routine motor and sensory nerve conduction studies on right side (median, ulnar, common peroneal and sural nerves) using standard procedures.

Assessment of sleep

It was done using the following scales: Pittsburgh Sleep Quality Index (PSQI) at admission [15]; and daily with Richard Campbell Sleep score [16]; and St Mary's Hospital Sleep Questionnaire [17]. Data from 30 patients was collected on 10 consecutive days with the sleep questionnaires following admission in the hospital. The first questionnaire was administered within 48 hours of admission.

- i) **Pittsburgh Sleep Quality Index (PSQI)** is a self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval. Nineteen individual items generate 7 "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Each component score ranges from 0 (no difficulty) to 3 (severe difficulty). The component scores are summed to produce a global score (range of 0–21);
- ii) **Richard Campbell Sleep score** consists of pictorial representation of 5 questions wherein patient marks or indicate mark on a line of 100 mm length with two ends of the line define extremes of answers of a particular question. Total Score is calculated by averaging the score on each line and is divided as good sleep (0-33 mm); moderate sleep (33-66 mm) and poor sleep (> 66 mm). In the current study, the original Richards score was modified for better understanding by the patient population i.e. score 0 was attributed to good sleep and score 100 to poor sleep, unlike the original scale, where scores are reverse; and
- iii) **St Mary's Hospital Sleep Questionnaire** consists of 14 questions regarding sleep onset, onset latency, number of awakenings, duration of sleep in day and night, depth of sleep, satisfaction after sleep, and causes of disturbed sleep if any. The score ranges from 6 to 39 with the higher score indicating better sleep.

Polysomnographic evaluation

All subjects underwent PSG at the sleep laboratory in the

department of Neurology according to the American Association of Sleep Medicine guidelines [18]. The PSG was reported following the AASM 2007 guidelines by a joint sitting of the investigators (KK, SS).

Statistical analysis

Data was analyzed using descriptive statistics such as Mean, SD, Minimum, Maximum values for continuous variables and frequency and percentage for categorical variables. Comparison between clinical variable groups and continuous sleep variables was done using independent sample 't' test. Association between categorical variables was analyzed by means of Chi Square test or Fisher's exact test. A $p < 0.05$ was considered statistically significant.

Results

Seventeen patients with GB syndrome presented in the 1st week, 8 in 2nd week and 6 in 3rd week of illness. Six patients were in the progressive phase at presentation. Antecedent events observed in 21/30 patients were: fever-70%, diarrhea-30%, and respiratory symptoms-12.5%. The distribution of limb weakness was: distal upper limb - 27, distal lower limb - 28, proximal upper limb - 25, and proximal lower limb - 28. Sensory symptoms included paresthesia in upper limb - 30, paresthesia in lower limb - 28, and pain - 30. Bulbar symptoms present in 23/60 patients were dysphagia - 5, poor cough - 6, dysphonia - 4. Neurological deficits consisted of facial paresis - 13, impaired joint position sense - 7, impaired vibration sense - 6, impaired pain - 4, and papilledema - 1. The severity of disease as per Hughes score and Modified Rankin's score is shown in table 1. Based on the HADS scale, anxiety and depression were present in 12 and 11 patients respectively. Serum CPK values ranged from 51 to 1688 IU/L (median: 265). The CSF cell count varied from 0 to 7 cells/cu.mm (mean: 0.85 ± 1.6) and protein ranged from 22 to 424 mg/dl (mean: 144.3 ± 108.3).

All patients were subjected to large volume plasma exchange on alternate day and 25 patients were given symptomatic therapy for pain viz. non-steroidal anti-inflammatory drugs (NSAIDs) -15 and antineuralgic agents - 22 (carbamazepine - 20; pregabalin - 2, duloxetine - 2, amitriptyline - 1 and tramadol - 1). Five patients did not receive symptomatic treatment.

Sleep disturbances

Pittsburgh Sleep Quality Index (PSQI): All patients were assessed by PSQI to ascertain their baseline sleep pattern i.e. before the onset of illness. Three (10%) patients had baseline sleep disturbances with a PSQI of >5 (Range 0-11, mean 1.62 ± 2.3). All the three patients

	Day 1 N (%)	Day 10 N (%)
Hughes grade		
4	19 (63.3)	15 (50)
3	6 (20)	7 (23.3)
2	3 (10)	4 (10)
1	2 (6.6)	2 (6.6)
Modified Rankin's score		
5	11 (36.6)	10 (33.3)
4	10 (33.3)	9 (30)
3	7 (23.3)	7 (23.3)
2	1 (3.3)	2 (6.6)
1	1 (3.3)	2 (6.6)
0	0	0

Table 1: Severity of illness on first (day 1) & last day (day10) of the study.

continued to have poor sleep during the acute phase of illness i.e. 10 days of hospitalization.

Richards Campbell score: Sixteen (53.3%) patients had poor sleep during their hospital stay as assessed by Richards score. The mean of the Richards score for all 60 patients on 10 nights was also calculated. It was observed that the sleep score was highest (poor sleep) on day 3 of evaluation and improved towards the last 3 days of evaluation i.e. 8th through 10th day. When the data was analyzed with respect to nights, abnormal Richard scores of >33 was recorded on 138 nights (46%) and a highly abnormal score of >66 was observed on 69 nights (23%) (Table 2).

St. Mary's score: Assessment of sleep disturbances was also performed by St. Mary's hospital sleep in any patients. Patients were also categorized on the basis of components of St. Mary's score viz. sleep onset latency, number of arousals and duration of sleep (Table 2). When these individual components were plotted with respect to day of illness, it was noted that the disturbances were maximum in the first week of illness.

Overnight polysomnography

The day of polysomnographic assessment ranged from 1st to 12th day of hospitalization and initial assessment (mean: 6.83 ± 3.07; median: 6.5).

Sleep macrostructure: The details of total time in bed, total sleep time, sleep efficiency, sleep onset, latency to various stages are provided in table 3. Sleep efficiency among patients was low with sleep efficiency of <85% being present in 28/30 patients. Twenty patients had sleep duration of less than 6 hours. Sleep onset latency >30 minutes was present in 4/26 patients. It is noteworthy that several patients did not

have all the stages of sleep: stage 1-2 patients, stage 3-6 patients, stage 4-13 patients and REM stage -7 patients. A significant observation was reduction of percentage (<5%) of REM sleep in 5 patients. There was no 'REM related behavior' noted.

Arousals: During the overnight PSG, 8 patients had frequent arousals. Maximum arousals were due to respiratory events and oxygen desaturation. (Table 4) The number of arousals among these patients was: ≤ 10:12; 11 to 20:10, 21 to 30:6 and >30:2. Six patients had abnormal arousal index i.e. >5 arousals/hour.

Periodic and isolated leg movements in sleep: Though seven patients had frequent periodic leg movements (PLMS), only three had abnormal PLMS index (5/hour) (Table 4).

Saturation parameters, heart rate and respiratory events in sleep and wake stages: The details are provided in tables 4 and 5. The abnormal apnea index i.e. apnea >5/hour was present in 3 out of 30 patients. Twenty one out of 30 patients had oxygen desaturation. Maximum frequency of desaturation events was in one patient (no.11) noted up to 116 times with a mean duration of desaturation being 49 seconds and desaturation index of 54.2 in him.

Correlation of factors responsible for sleep disturbances

The total sleep time was calculated in younger (<40 years: <6 hours-13; >6 hours: 10) and older (>40 years: <6 hours-7; >6 hours: 0) and it was noted that none of the older patients slept >6 hours (p=0.03). The sleep latency (<30 mins or >30 mins) and total sleep time were not affected by factors like anxiety, severity of illness (Hughes scale: 1-3 vs. 4-5; Rankin scale: 1-3 vs. 4-5), visual analogue scale for paresthesia (Vapar ≤ 5 or >5); Visual analogue scale for pain (Vap ≤ 5 or >5); and Verbal rating scale for pain (Verp ≤ 5 or >5). However presence of

Sleep Question Score	Day of hospitalization	1	2	3	4	5	6	7	8	9	10
Richards Campbell score	Mean ± SD	42.8 ± 36.8	43.8 ± 28.7	47.4 ± 31.5	48.08 ± 32.8	44.02 ± 29.5	43.2 ± 30.01	38.6 ± 27.3	35.1 ± 27.9	35.71 ± 27.68	35.04 ± 29.5
	>33	14	13	17	16	15	15	15	12	10	11
St Mary's sleep score	Mean ± SD	23.9 ± 9.1	22.6 ± 9.04	21.4 ± 9.06	23.03 ± 9.2	21.3 ± 9.4	22.1 ± 9.3	23.7 ± 8.6	25.57 ± 8.7	26.64 ± 8.7	25.7 ± 8.9
	Sleep onset latency>30 min	9	10	12	9	10	10	7	7	4	9
	Frequent arousals (>2)	12	12	14	13	14	15	12	9	8	7
	Duration of sleep <6 hrs	14	17	18	18	18	18	17	15	15	12

Table 2: Richards Campbell & St Mary's sleep score on consecutive 10 nights.

Sleep parameters	Minimum	Maximum	Mean	SD
Time In Bed (TIB) (min)	266.70	541.30	466.86	59.91
Total Sleep Time (min)	48	495.50	297.49	106.81
Sleep Efficiency (%)	18	96.50	61.88	18.65
Sleep Onset (min)	0	116	22.94	26.18
Latency to stage 1 (min) [n=28]	1.5	394.7	110.2	112.2
Latency to stage 2 (min) [n=30]	0	271.00	36.6	54.5
Latency to stage 3 (min) [n=24]	12	325.3	72.8	62.3
Latency to stage 4 (min) [n=17]	0	165.00	73.2	48.4
Latency to stage REM (min) [n=23]	0	273.00	136.5	76.3
% in stage 1 [n=28]	2	38	11.78	8.38
% in stage 2 [n=30]	39.2	100	71.52	14.31
% in stage 3 [n=24]	0.30	22.90	8.52	5.11
% in stage 4 [n=17]	1.10	23.20	7.01	6.75
% in stage REM [23]	1.40	18.30	8.57	5.21

Table 3: Polysomnographic variables showing sleep macrostructure in patient population.

Arousal events	Minimum	Maximum	Mean±SD
Arousal number	3	104	18 ± 18.41
Arousal index	0.5	18.2	4.36 ± 4.29
Arousal due to desaturation	0	52	2.10 ± 9.46
Arousal due to apnea	0	57	3.47 ± 10.63
Arousal due to snoring	0	4	0.13 ± 0.73
Arousal due to desaturation- index	0	24.30	0.93 ± 4.42
No. of PLMs	0	49	6.4 ± 11.84
PLMs index	0	7.30	1.23 ± 1.97
No. of Isolated leg movements	0	14	3.20 ± 4.13
Isolated leg movements index	0	2.90	0.64 ± 0.75
No. of Isolated leg movements with arousal	0	2	0.20 ± 0.48
Arousal due to PLMs	0	4	0.7 ± 1.15
Arousal due to PLM - index	0	0.9	0.16 ± 0.25
Arousal due to apnea - index	0	26.60	1.25 ± 4.84
Arousal due to snore index	0	0.9	0.03 ± 0.16
Apnea index total	0.0	44.40	3.47 ± 9.43
Hypopnea index total	0.0	15.40	2.01 ± 3.63
Apnea- hypopnea index total	0.0	59.80	5.5 ± 12.62
Arousal due to obstructive apnea	0.0	2.80	0.32 ± 0.65
Arousal due to mixed apnea	0.0	15.40	0.52 ± 2.81
Arousal due to central apnea	0.0	8.40	0.40 ± 1.61
Arousal due to hypopnea - index	0.0	2.30	0.15 ± 0.43

Table 4: Arousals in sleep and the events responsible for arousals.

Saturation parameters and Heart rate	Minimum	Maximum	Mean ± SD
Awake minimum saturation	87	96	92.70 ± 7.48
Awake maximum saturation	96	103	98.86 ± 1.43
Awake average saturation	91.30	98.30	95.60 ± 1.76
Sleep minimum saturation	61	95	96.93 ± 7.81
Sleep maximum saturation	95	104	98.36 ± 1.56
Sleep average saturation	90.20	98.20	94.91 ± 2.13
Awake minimum heart rate	42	104	67.60 ± 15.14
Awake maximum heart rate	84	182	117.50 ± 18.94
Sleep minimum heart rate	40	103	66.43 ± 13.92
Sleep maximum heart rate	94	151	105.67 ± 24.39
Sleep average heart rate	48.30	111.60	80.08 ± 14.65

Table 5: Saturation parameters and heart rate in sleep and wake stages.

depression did not influence sleep latency it certainly reduced sleep total time ($p=0.049$).

Discussion

Sleep disturbances have been recorded in patients with diabetic neuropathy, multifocal motor neuropathy [3] and are attributed to pain, paraesthesia, restless leg syndrome and depression [1,19]. GB syndrome is the most severe form of polyneuropathy with variable sensory symptoms and motor disability and the need for hospitalization with uncertainty of the course of the disease. Thus sleep disturbances are expected in GB syndrome. This study evaluated polysomnographic (PSG) profile of 30 patients with GBS shortly after hospitalization, irrespective of the day of illness.

Phenotype

All patients had quadriparesis with distal (90-93%) more than proximal weakness (77-91%). Sensory symptoms viz. paresthesia (90%) and pain (95%) were rather frequent, probably due to prospective and daily evaluation of sensory symptoms for ten consecutive days. Other phenotypic features were similar to earlier reports [20-22].

Questionnaire based sleep disturbances

A total of 16 patients had poor sleep during their hospital stay as assessed by Richards scale. Three of these patients had baseline poor quality of sleep (PSQI>5) thus 13 patients with baseline good sleep developed sleep disturbances during the acute phase of illness. Richard's scale consists of visual analogue scale. It is easy to administer and enables objective comparison between patient populations. According to Richards score, 16 patients had a poor sleep. Of the 297 nights studied (data of 3 nights were not available due to early discharge from hospital) poor sleep was reported on 138 nights (46%). Sleep disturbances in hospitalized patients could be due to various factors like paresthesia, pain, immobility, anxiety/depression, plasmapheresis, untimely injections, shift from one ward to other, hospital schedule like checking of vitals, diagnostic procedures, type of facility like general or special ward with privacy matters, disturbances from other patient e.g. shouting and snoring, death of the other patient(s) and others. Patients were asked these questions every day and also given option to cite any other reason that believe could have caused sleep disturbances.

In this study, St Mary's Hospital sleep Questionnaire was used to evaluate nature of sleep disturbances. An abnormal sleep onset latency of >30 min was noted on day 3. The common reasons reported by patients were pain, paresthesia, and immobility causing difficulty to turn around in bed or need for going to toilet. The environmental disturbances like hospital schedule, presence of other patients, new place, and transfer were less frequently reported in the current study. This is in contrast to other studies where sleep in hospitalized patients was significantly affected due to environmental disturbances [23]. Most of the studies about sleep disturbances in hospitalized patients have evaluated patients in acute care settings like post cardiac surgery patients or in intensive care units. Interestingly, patients with less sensory symptoms and minimal motor disability complained more about the environmental disturbances. The effect of pain on sleep latency has been studied in various studies [24]. Frequent awakening i.e. arousals of >2 in night time was considered abnormal. The maximum number of patients experienced frequent awakenings on day six of the study. On an average, 12 patients had sleep fragmentation. Most of the patients attributed sleep fragmentation to pain (7/10 nights), paresthesia (7/10 nights), anxiety/depression (5/10 nights), frequent desire to pass urine, cough, and environmental disturbances.

Polysomnography

The results of PSG revealed reduced sleep efficiency in patient population. Sleep efficiency of >85% is considered normal. Only 2 patients had good sleep. Frequent arousals, long latency to sleep after arousal or prolong sleep onset were responsible for reduced sleep efficiency. All the patients had >2 arousals during the sleep.

In this study, sleep architecture of patients was deranged with increase in Stage 1 and 2, reduced REM and stage 4 percentages. Seven patients had absent REM. All these changes may happen in persons suffering from depression or chronic pain disorders [24]. On assessing sleep parameters among depressed and non-depressed individuals, total sleep time was decreased in depressed individuals. However, other parameters like sleep fragmentation and duration of sleep were equally distributed in depressed and non depressed group. This differential effect of depression requires further studies. Similarly, there was no difference in sleep parameters in groups with presence of anxiety, disability, higher pain and paresthesia scores. This suggests that GBS per se may give rise to certain sleep abnormalities independent of the co-morbid factors. The current study has revealed abnormal sleep

onset latency in 4 out of 30 patients. These patients were in age of 16 to 25 years. This supports the observations in the meta-analysis that PSG recorded sleep onset latency is unchanged irrespective of the age [25]. The distribution of these factors in sleep related abnormalities are equal implying unknown mechanism in GBS may be responsible for sleep disturbances that require exploration.

Cochan et al. evaluated 139 patients of GB syndrome with or without mental status abnormalities admitted to ICU [7]. The abnormalities were: with sleep onset REM (83%), abnormal eye movements during non-REM sleep (57%), high percentages of REM sleep without atonia ($92 \pm 22\%$), REM sleep behavior disorders and autonomic dysfunction (100%), and reminiscent of a status dissociatus. The patients in this cohort were not admitted to ICU and did not have REM associated behavioral issues or any other mental status abnormalities during sleep.

Pathophysiology of sleep disturbances in GB syndrome

The exact mechanism of sleep disturbances in GB syndrome is unknown and speculative. There could be variable combination of peripheral and central mechanisms. These patients experience sensory disturbances including pain, have recent onset motor disability, require prolonged hospital stay and exhibit anxiety regarding uncertain course of the disease and may be expected to have sleep disturbances.

The CSF hypocretin-1 (a hypothalamic neuropeptide deficient in narcolepsy) levels, measured in 20 patients, were lower in patients of GBS with hallucinations (555 ± 132 pg/ml) than in those without (664 ± 71 pg/ml, $p=0.03$). The authors proposed involvement of lateral hypothalamus in GB syndrome that governs the sleep architecture. This may be due to its location where the blood brain barrier is exposed to antibodies circulating in blood. Thus GB syndrome may also have putative antibodies against central targets [26]. There are studies reporting CNS involvement in GB Syndrome [27]. It has been postulated that dreamlike and other hallucinatory experiences may occur when there is a disruption in the "corollary discharge" system that allows us to discriminate between self-generated and externally generated neural activity [28]. The sensory and motor denervation that occurs in GB syndrome might allow the same confusion between internally and externally generated thoughts and sensations that occur in sleep, resulting in thoughts having a dreamlike or hallucinatory quality [29]. The possible explanations for CNS involvement in GBS include watershed infarction, demyelination, reversible posterior leukoencephalopathy, and adverse effects of immunoglobulin, status dissociatus [27,30]. These aspects were not studied here.

This comprehensive study is first of its kind where qualitative and quantitative evaluation of sleep disturbances was done in GB syndrome in a prospective manner. Sleep disturbances and altered architecture in GBS may be multifactorial and may include many unidentified factors which require further studies. Inclusion of control group will strengthen the result. Treatment of underlying causes like pain, anxiety; early institution of specific treatment for GB syndrome like plasma exchange or IVIg and reassurance might be some of the steps in alleviating the sleep disturbances. Systematic enquiry, evaluation and treatment of sleep disturbances may reduce morbidity and improve quality of life.

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