The Sleep Laboratory Findings in Kleine-Levin Syndrome: Temporal Variations of Sleep Structures

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Abstract

**Introduction:** Kleine-Levin syndrome (KLS) is a rare disorder affecting predominantly male adolescents. This disorder is characterized by recurrent hypersomnia accompanied by hyperphagia and abnormal behavior, mainly in the form of hypersexuality. The cause and pathogenesis remain unknown. There is only scant information on the sleep characteristics in KLS patients. This study describes findings from polysomnography (PSG) and Multiple Sleep Latency Test (MSLT) and the relationship between clinical presentation and PSG findings in a relative large group of KLS patients followed at a single place.

**Method:** 19 patients (17 males and 2 females) with KLS were investigated with PSG and MSLT. 9 patients had complete data during symptomatic episode and the asymptomatic interval. The difference of sleep pattern in both periods was compared. In addition, we closely examined the correlation between the structure and time course of the symptomatic period.

**Results:** When PSG were performed during the first half of the symptomatic period there was always a reduction in slow wave sleep (SWS) with a progressive return to normal in the second half, despite persistence of clinical symptoms. In the second half of the symptomatic period percentages of SWS were very similar to those monitored during the asymptomatic period. On the other hand, rapid eye movement (REM) sleep
remained normal in the first half of the episode but decreases in the second part, with statistically significant difference (Mann-Whitney test): SWS (p=0.014) and REM (p=0.027) between first and second half of episodes. MSLT showed that 7 of 17 patients had sleep onset in REM ≥ 2 and the overall mean sleep latency was 9.51±4.82 minutes.

**Conclusion:** Defining the precise time for PSG investigation is of paramount importance. As findings vary overtime during each episode, a clear reduction of SWS close to the onset of symptoms accompanied the opposite behavior of REM sleep. MSLT is of little help and findings appear to be unrelated to time of onset of symptoms.

**Keywords:** Kleine-Levin syndrome, periodic hypersomnia, polysomnography, multiple sleep latency test, lithium
Introduction

The Kleine-Levin syndrome (KLS) is a rare disorder with onset during teenage years.\textsuperscript{1-4} It was first reported by Kleine\textsuperscript{5} in 1925 and seen mostly in males, but female\textsuperscript{4} and middle age adult-onset cases have been reported.\textsuperscript{6-12} The diagnosis of KLS is still based on the clinical presentation now. Levin emphasized the association of periodic somnolence with morbid hunger in 1936.\textsuperscript{13} From the original strict criteria to gradually broadened criteria, there is a lot of controversy for the diagnosis of KLS. At present, the essential clinical criterion of KLS noted in International Classification of Sleep Disorder, 2\textsuperscript{nd} ed. (ICSD-2) is recurrent episodes of hypersomnia. Moreover, patients have to experience at least one of those symptoms only during the episodes which may include binge eating, hypersexuality, abnormal behavior such as irritability, aggression and odd behavior and cognitive abnormalities such as feeling of unreality, confusion, and hallucination.\textsuperscript{14}

The etiopathogenesis of KLS is still unknown. The triggering factors such as infection or fever, substance (alcohol or marijuana), head trauma, sleep deprivation, stress, menses, and miscellaneous have been reported.\textsuperscript{15} However, hypothalamic or circadian dysfunction, abnormalities in serotonin and dopamine metabolism were reported in a few cases.\textsuperscript{16-23} Therefore, a neurotransmitter imbalance in serotonergic or dopaminergic pathway is hypothesized.\textsuperscript{18,21} Recently, the possible presence of an
autoimmune process was investigated. In 13 case reports, the DR2 phenotype was positive in four cases.\textsuperscript{24-27} In a controlled series of 30 European patients, the DQB1*0201 genotypic allele was twice more frequent in the KLS patients.\textsuperscript{28} As to the neuropathologic findings of brain, that had been revealed intense signs of inflammatory encephalitis with in the hypothalamus and thalamus.\textsuperscript{8, 21} The SPECT findings of the hypoperfusion were seen in basal ganglion, cortex, and thalami.\textsuperscript{29}

A limited number of articles with sleep laboratory study have been performed by far. Nocturnal polysomnography (PSG) indicates reduced sleep efficiency and increases wake time after sleep onset. Mayer et al. reported that decreased sleep efficiency and slow wave sleep in his case reports.\textsuperscript{22} Gadoth et al. also showed decreasing sleep efficiency and frequent awakening from sleep stage 2.\textsuperscript{30} Rosenow and Arnulf have reported that abnormal sleep latency in the multiple sleep latency test (MSLT) results.\textsuperscript{31, 32} However, there is still a debating on sleep laboratory findings. The controversy findings may be due to the timing of examination or patient’s willingness to comply with the procedure. We reported 19 patients of KLS and analyzed their sleep laboratory findings during symptomatic episodes and asymptomatic intervals. Furthermore, the previous arguments of the sleep pattern change during episodes would be discussed and described in detail.
Patients and methods

Between 2001-2007, 25 Taiwanese patients were diagnosed with KLS according to the ICSD-2 criteria and they comprised our study population in the Sleep Center of Chang-Gung Memorial Hospital. All patients presented with behavioral hypersomnia and were sporadic. The demographic and clinical data of the patients are shown in Table 1. There are 25 males and 3 females, and the sex ratio showed a large predominance of men. The symptoms onset of the patients was between 9.6 and 15.4 years with a mean age at onset of 12.5 years. They presented with a minimum of 1 and a maximum of 8 symptomatic episodes per year. The duration of each episode was variable within and between subjects, from 2 to 23 days.

Admission and outpatient charts were reviewed and details in the clinical and laboratory work-up were tabulated. The original polysomnographic (PSG) and multiple sleep latency test (MSLT) recordings were obtained. Polysomnography was recorded with electroencephalogram (EEG), electrooculaogram (EOG), electromyogram (EMG), electrocardiogram (EKG) and pulse oxymetry. Standard polysomnography recording and scoring methods according to Rechtshaffen and Kales were applied.  

Subjects, particularly those with long-term follow-up, had received treatment trials that included lithium, imipramine, fluoxetine, moclobemide, risperidone,
methylphenidate, modafinil, acetazolamide, carbamazepine, and influenza type A vaccine. None of the treatment trials had an impact on the duration of the episode or prevented a relapse. All patients except one still with lithium treatment were drug-free at least one week before PSG or MSLT recording. Prior to sleep laboratory studies, all subjects had normal urine and blood tests, including C-reactive protein. IgG and IgM antibodies in serum and cerebrospinal fluid were evaluated at the first symptomatic episode to rule out viral infection or immunologic disorders.

19 patients were evaluated PSG and MSLT during a symptomatic episode (table 2-1). 10 PSG records were obtained recording during both symptomatic and asymptomatic periods, while 7 were obtained only during attacks. Similarly, 8 MSLT records were obtained recording during both symptomatic and asymptomatic periods, while 9 were only obtained during attacks. There were 4 patients recorded during two attacks. For uniformity, the first night effect and the gray area between symptomatic and asymptomatic periods were also considered, the 2 patients had the extra recording at the end of episode of were not used and only the results of the second were used for statistical analysis (Table 2).

In comparing sleep characteristics during and between attacks, we analyze 9 patients with PSG and 7 with MSLT who were recorded both during and in-between an attack and all of them were drug-free at least two weeks before recording. To
explore the drug effect on the abnormal sleep pattern, the patient with lithium therapy
during symptomatic period was not included in the comparison of PSG and MSLT.
As well as other studies of MSLT, 17 patients with MSLT during episodes were
utilized to assess the sleepiness in KLS. Because of the small sample size, statistical
analysis used Wilcoxon signed-rank test performed for investigation during
symptomatic and asymptomatic periods, and Mann-Whitney U test for the proportion
of baseline value of different patients in the first and second half part of the episodes.
Results

Polysomnography

In the 19 patients had PSG and MSLT studied, none was found to have either sleep apnea or periodic limb movements. Electroencephalogram (EEG) awake and asleep, CT scan, and MRI were all read as normal.

Comparing sleep structures during and between episodes, there was no statistically significant difference for any sleep stage or efficiency. (Table 3) The decreased tendency of slow wave sleep (SWS) and stage rapid eye movement (REM) were noted. (P value of SWS and REM were respectively 0.066 and 0.086)

In order to evaluate these sleep characteristics vary overtime, the time course is presented as the duration between the PSG investigated day and the onset of the episode divided by the total duration of the episode. The results were also compared during first and second half of symptomatic episode (Mann-Whitney U test). Moreover, all sleep laboratory parameters were corrected as proportion of baseline value, i.e. the result during symptomatic episode divided by that in asymptomatic period. (Table 4) Therefore, the ratio (proportion of baseline value) around 1 means that results are equal during episodes and between asymptomatic interval.

The proportion of baseline SWS value was reduced during the first half of episodes, with a progressive return to normal during the second half despite
persistence of clinical symptoms. The reduced SWS proportion (0.50±0.21) means only half amount of the normal rage SWS in the former episode with significant difference (p=0.014). Furthermore, there was an upward tendency around the middle of episodes. (Fig 1) In opposition, REM sleep remained normal in the first half of the episodes (proportion of baseline REM value was 1.01±0.10), and decreased in the second part (0.72±0.13) with significant difference (p=0.027). However, the SWS decrease during the first half is more than REM in during the second. (Fig 2)

Overall sleep efficiency was poor (78.0±16.0%) during SMP and it is worse during the first half (the proportion was 0.90±0.15). However, it remained abnormal (80.4±20.2) and much more variable during asymptomatic periods. (Table 3 and 4)
Curve fit for proportion of baseline SWS and REM value

According to the step-like distributions of experimental data given here (SWS and REM versus time), two proper equations, $y = a_s + b_s \cos^{m_s}\left[\frac{\pi}{2} (1 - x)^{n_s}\right]$ and $y = a_r + b_r \cos^{m_r}\left(\frac{\pi}{2} x^{n_r}\right)$, are adopted to fit them respectively. Let $Y(x_i)$ represent an experimental value, and let $y(x_i)$ be a value from a preferred fitting equation where $x_i$ is a particular value of the variable assumed to be free of error. The least-squares criterion requires that $\text{error} = \sum_{i=1}^{N} [Y(x_i) - y(x_i)]^2$ be a minimum where $N$ is the number of data points. After reaching the minimum by suitable choice of the parameters such as $a_s, b_s$, etc., we have $y = 0.32 + 0.84 \cos^{27}\left[\frac{\pi}{2} (1 - x)^3\right]$ for SWS vs. time with error = 0.2296 (Fig.1) and $y = 0.63 + 0.46 \cos^{33}\left(\frac{\pi}{2} x^3\right)$ for REM vs. time with error = 0.0501 (Fig.2).
Multiple Sleep Latency Test

MSLT of 7 patients with complete data showed no statistically difference (Wilcoxon signed-rank test) in mean sleep latency and number of SOREM between symptomatic and asymptomatic period (Table 5). However, the mean sleep latency during episodes (10.60±5.81 min.) is more variable than asymptomatic interval (10.13±3.61 min.) 5 of the 7 patients were investigated during the second half of SMP and the proportion of baseline MSLT were around 1 (1.12±0.10), i.e. their mean sleep latency between symptomatic and asymptomatic period were nearly equal. The other 2 of 7 patients were investigated during the first half part, and one patient recorded on the 3rd day of 14 day-episode showed mean sleep latency was 0 minute. Because of his extremely hypersomnia that he can not be aroused to follow the MSLT procedure.

The presentation only during episodes was also analyzed. In 17 patients with MSLT recording, mainly (12 of 17) investigated during the second half of episodes, the mean sleep latency of 3 (17.6%) patients was < 5 minutes, 7 (41.2%) between 5-10 minutes, and 7 (41.2%) > 10 min. The overall mean sleep latency was 9.98±4.90 min. Furthermore, 7 patients had number of SOREM ≥ 2 but only 2 (11.8%) patients fit the pattern (mean sleep latency < 8 min and number of SOREM ≥ 2) of narcolepsy diagnostic criteria without cataplexy or sleep paralysis. 14
Discussion

Polysomnography

This series of 25 patients is the first relative large group of KLS patients in whom complete sleep laboratory data with precise investigated timing recording were studied. The results of the MSLT and PSG depend on the timing of the tests during an episode have also been noted by Rosenow et al. They recommend that PSG during a symptomatic episode should not be performed before the second night of an episode and more than 2 weeks after symptomatic episode to represent the asymptomatic interval, because pathologic PSG changes precede an episode by 2 weeks and persist for 1 week. In another polysomnographic meta-analysis of KLS patients, the variability and highly dependence on the delay between the onset of the episode and the laboratory test were also reported.

In order to explore the sleep structure changes relative to time, the definition of episodes onset and off is based on whether the patients have functional impairment or not. Usually, the exact time of an episode starts when patients can not go to school. Although patients were gradually back to their baseline behavior on the last few days of episodes, we define the end of the episode when they can return to school.

In the 9 patients with PSG complete data, there are 5 patients during the first half and 4 patients in the second part. Comparing the overall SMP and ASM, the reduced
SWS without significant difference account for more patients in the first half of SMP, while the less REM decrease may be due to fewer patients in the second part and the degree of REM decrease (72±12%) less than SWS reduced (50±21%) is hard to detect.

The significant difference in the SWS and REM between the first and second half of SMP is very useful to resolve the argument of the sleep structure abnormalities. Most studies about polysomnographic findings in KLS showed decreased SWS during SMP probably because of the majority PSG recorded during the first half of SMP while fewer reports announced decreased REM without SWS reduced account for the majority PSG recorded during the second half and the hardly detectable decrease. In addition, no report documented that both SWS and REM decrease. It also support that the SWS and REM reduced in the different pathological stage.

However, there is a transitional stage around the middle of episodes and the polysomnographic characteristics are ambiguously belong to the first or second half of an episode. An amply recording of a 16-year-old boy revealed the proportion of baseline SWS and REM value of 51.7 % (14.0min/27.1min.) and 92.4 % (19.4min./21.0min.) This result with obviously reduced SWS and mild decrease REM belong to the first half part of episodes in our observation, was demonstrated on the
4th day of his third episode lasting for 6-7 days.\textsuperscript{31} It should be explained as different definition of the episode onset and off or the notable systemic error and variation of a relative short symptomatic period.

The low efficiency (78.0±16.0) during symptomatic episodes remained abnormal (80.0±20.2) during asymptomatic interval. As well as the findings have been reported by Dauvilliers et al. and the low sleep efficiency were similar. Another statistically significant difference was found for sleep efficiency decrease during the attacks in independent samples.\textsuperscript{30} It was interpreted as frequent awakening from sleep stage 2.\textsuperscript{39} In contrast, high sleep efficiency was considered a feature of polysomnographic findings in the previous edition ICSD.\textsuperscript{40} A short-lasting insomnia was also noted in our patients at the end of an episode as other reports.\textsuperscript{41-43} In our opinion, because of the first night effect and variability of every patient, comparison of the sleep efficiency changes between symptomatic episodes and asymptomatic interval should be very difficult.
Multiple Sleep Latency Test

In recent years several authors have reported comparisons of MSLT of KLS during symptomatic and a symptomatic periods in single cases.\textsuperscript{12, 31, 38, 44, 45} Most results indicate short sleep latencies and sleep onset REM (SOREM) during spontaneous daytime naps but not during the interval.\textsuperscript{38, 44, 45} The mean sleep latency during the episodes less than 5 minutes had commonly been reported.\textsuperscript{12, 31, 32} Meanwhile, Rosenow et al. observed that the mean sleep latency increases gradually along with the course (episode, end of episode, interval) while the number of SOREM decreases.\textsuperscript{31}

In our group 17 patients with MSLT, mainly investigated during the second part of episodes, revealed the mean sleep latency was 9.51±4.82 and there were no significant difference during asymptomatic interval. Moreover, 41.2\% patients had SOREM $\geq$ 2 but only 11.8\% fit the pattern of narcolepsy diagnostic criteria. This result is similar with other reports.\textsuperscript{31, 32} These MSLT features indicate the main symptom of KLS patients during the second half of episodes are fatigue rather than hypersomnia and the daytime sleepiness pattern differed from narcolepsy. As well as the statement by Arnulf et al. that sleep symptoms changed from frank hypersomnia during the first episodes to a heavy fatigue accompanied by a feeling “as if in twilight between sleep and waking” during later episodes.\textsuperscript{32} We agree the comment of ICSD-2
that results of the MSLT are highly dependent on the subject’s willingness to comply
with the procedure.\textsuperscript{14}
Sleep laboratory findings of a patient with lithium therapy during episode

Since KLS shares some similarities with bipolar disorder especially cognitive and behavioral abnormalities, such as irritability and hypersexuality, various mood stabilizers were used. Only lithium had a reported response rate significantly higher than medical abstention.\(^9, 22, 28, 31\) Patients who were treated with lithium showed a marked decrease in frequency of episodes.\(^28\) In recent years several authors have reported on lithium’s usefulness as the prophylactic drug.\(^23, 25, 37, 46-48\)

To our knowledge, only one report studies the polysomnographic characteristics of KLS patients on literature\(^37\) but no MSLT study. The patient with lithium therapy had PGS performed on the 6\(^{th}\) day of a 10-day episode, which belong to the second half of episode characterized by reduced REM sleep time. The proportion of baseline REM and SWS are respectively 65% and 95%, which fit the regression model and are close to the result of a patient with similar investigated time (day/duration) = 0.58 (7/12). (Fig. 1 and 2) Meanwhile, the MSLT showed mean sleep was 4.7 min. with 3 SOREM.

Poppe et al reported four patients were investigated with maintenance of lithium medication for up to 36 months and serum levels between 0.6-0.9 mmol/l were attained. Polysomnographic findings during SMP also revealed reduced REM sleep time with unremarkable SWS change.\(^37\) The agreement with our observation implied
that lithium therapy decreases duration and frequency of episodes in KLS but seems not effective in the abnormal sleep structure. However, compared with the clinical presentation the last four years prior to lithium therapy in our patient, lithium also definitively improved the behavioral disturbance and psychiatric symptoms during symptomatic episodes as other reports.\textsuperscript{49} Therefore in KLS with a high frequency of episodes and severe behavioral-emotional disorder, lithium is still suggested as one of the most effective treatment.\textsuperscript{25, 32, 37, 50, 51}
Conclusion

Defining the precise time for PSG investigation is of paramount importance. As findings vary overtime during each episode, a clear reduction of SWS close to the onset of symptoms accompanied the opposite behavior of REM sleep. MSLT is of little help and findings appear to be unrelated to time of onset of symptoms. These polysomnographic characteristics are usefully objective indicator for not only the pathogenesis of clinical course but also pharmacological effect in Kleine-Levin syndrome.
Acknowledgments

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References


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Tables and Figures

**Table 1** Demographic and clinical data of 10 Kleine-Levin syndrome patients with complete data

<table>
<thead>
<tr>
<th></th>
<th>Mean±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset (years)</td>
<td>12.5±1.8</td>
<td>9.6-15.4</td>
</tr>
<tr>
<td>Mean time in bed (hours)</td>
<td>19.7±3.4</td>
<td>10-23</td>
</tr>
<tr>
<td>Duration of episodes (days)</td>
<td>11.2±3.5</td>
<td>2-23</td>
</tr>
<tr>
<td>Number of episodes per year</td>
<td>3.6±1.4</td>
<td>1-8</td>
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</table>

**Table 2-1** Timings of polysomnography (PSG) recordings in 19 patients with Kleine-Levin syndrome

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Recordings during symptomatic episodes</th>
<th>Recordings during asymptomatic period</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>13</td>
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</table>

**Table 2-2** Timings of multiple sleep latency test (MSLT) recordings in 19 patients with Kleine-Levin syndrome

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Recordings during symptomatic episodes (SMP)</th>
<th>Recordings during asymptomatic period (ASM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>11</td>
</tr>
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</table>
Table 3 Polysomnographic characteristics during symptomatic episodes and asymptomatic period in 9 patients with Kleine-Levin syndrome

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic episodes</th>
<th>Asymptomatic period</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 / TST (%)</td>
<td>18.0±10.2</td>
<td>12.6±9.1</td>
<td>0.173</td>
</tr>
<tr>
<td>Stage 2 / TST (%)</td>
<td>47.0±11.9</td>
<td>42.9±9.1</td>
<td>0.314</td>
</tr>
<tr>
<td>Stages 3-4 / TST (%)</td>
<td>19.1±10.2</td>
<td>26.2±7.6</td>
<td>0.066</td>
</tr>
<tr>
<td>REM sleep / TST (%)</td>
<td>15.9±4.5</td>
<td>18.3±4.5</td>
<td>0.086</td>
</tr>
<tr>
<td>EFF(%)</td>
<td>78.0±16.0</td>
<td>80.4±20.2</td>
<td>0.594</td>
</tr>
<tr>
<td>TST (min)</td>
<td>289.2±74.8</td>
<td>298.4±67.5</td>
<td>0.441</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD with Wilcoxon signed-rank test used due to the small sample size.

Table 4 SMP/ASM ratio between the first and second half symptomatic episodes

<table>
<thead>
<tr>
<th>SMP/ASM ratio</th>
<th>During the former half episodes</th>
<th>During the later half episodes</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>2.20±1.30</td>
<td>1.60±1.13</td>
<td>0.462</td>
</tr>
<tr>
<td>Stage 2</td>
<td>1.13±0.44</td>
<td>1.13±0.26</td>
<td>0.806</td>
</tr>
<tr>
<td>Slow Wave Sleep</td>
<td>0.50±0.21</td>
<td>1.07±0.15</td>
<td>0.014*</td>
</tr>
<tr>
<td>REM</td>
<td>1.01±0.10</td>
<td>0.72±0.13</td>
<td>0.027*</td>
</tr>
<tr>
<td>Efficiency</td>
<td>0.90±0.15</td>
<td>1.24±0.62</td>
<td>0.806</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD with Mann-Whitney U test used due to the small sample size. SMP refers to symptomatic period; ASM, asymptomatic period. *P < 0.05
**Table 5** Multiple Sleep Latency Test during symptomatic episodes and asymptomatic period in 7 patients with Kleine-Levin syndrome

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic episodes</th>
<th>Asymptomatic period</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean sleep latency (minute)</td>
<td>10.13 ± 3.61</td>
<td>10.6 ± 5.81</td>
<td>0.237</td>
</tr>
<tr>
<td>Number of sleep onset in REM (SOREM)</td>
<td>1.14 ± 1.07</td>
<td>1.14 ± 0.60</td>
<td>1</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD with Wilcoxon signed-rank test used due to the small sample size.

**Figure 1** Proportion of baseline slow wave sleep (SWS) value (i.e. SWS percentage during symptomatic episodes divided by SWS percentage during asymptomatic period) in 9 patients. The time course is presented as the duration between the PSG investigated day and the onset of the episode devided by the total duration of the episode. The red spot represent the patient with lithium therapy during episode.

**Figure 2** Proportion of baseline rapid eye movement stage (REM) value. The red spot represent the patient with lithium therapy during episode.