ORIGINAL ARTICLE

Benign EEG variants in the sleep—wake cycle: A prospective observational study using the 10—20 system and additional electrodes

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Abstract
Objectives. — To study the prevalence of benign EEG variants (BEVs) in the sleep—wake cycle among 1163 consecutive patients.
Methods. — Prospective, observational EEG study using the 10—20 system with systematically two additional anterior-temporal electrodes. Depending on clinical indications, other electrodes were added. REM sleep identification was based on its characteristic EEG graphoelements and rapid eye movements, clearly detectable with the additional anterior-temporal and fronto-polar electrodes due to eye proximity. The video-EEG monitoring duration was between 24 hours and eight days.
Results. — We identified 710 patients (61%) with BEVs. Positive occipital sharp transients of sleep (POSTs) were observed in 36.4% of participants, mu rhythm in 22.4%, lambda waves in 16.7%, wicket spikes (WS) in 15%, 14- and 6-Hz positive bursts in 8.3%, benign sporadic sleep spikes (BSSS) in 3.3%, rhythmic mid-temporal theta burst of drowsiness (RMTD) in 2.15%, midline theta rhythm in 2.1% and six-Hz spike and wave (SW) bursts in 0.1%. WS and RMTD were present

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Introduction

Benign EEG variants (BEVs), often referred to as "benign epileptiform variants", are unusual physiological activities, often with sharp morphology. As "epileptiform" is an ambiguous term, this term must be discouraged.²⁰ BEVs include mu rhythm, lambda waves, positive occipital sharp transients of sleep (POSTs), midline theta rhythm, wicket spikes (WS), rhythmic mid-temporal theta burst of drowsiness (RMTD), subclinical rhythmic electrographic discharge of adults (SREDA), benign sporadic sleep spikes (BSSS), 14- and 6-Hz positive bursts and six-Hz spike and wave bursts. Some examples of BEVs are shown in the supplementary material. It is important to be well acquainted with the morphology because BEVs are often sharply contoured and could be mistaken for epileptiform activity. The accurate interpretation of these BEVs is essential to avoid overinterpretation leading to a wrong diagnosis of epilepsy,²¹,²⁸ or the incorrect diagnosis of the type of epilepsy.²²

The prevalence of BEVs is not well known. Some are considered rare, but only waking EEGs, or EEGs with a short period of sleep, have been studied. Firstly, the detection of BEVs depends on the type of EEG recording (standard versus prolonged EEG) and the sleep duration. Fourteen- and 6-Hz positive bursts, BSSS, and POSTs are exclusively seen during sleep. WS generally occurs during drowsiness and light sleep and disappear during deep sleep, but may reappear during REM sleep.¹⁴,²⁹ Secondly, the studied population is important. Fourteen- and 6-Hz positive bursts,⁴⁰ and POSTs¹⁰ are mainly seen in younger people, whereas SREDA mainly occurs in individuals over 50 years.⁴² Thirdly, reduced EEG montages fail to detect BEVs correctly. The application of a lower temporal electrode chain that explores the inferior part of the temporal lobe significantly increases the detection of 14- and 6-Hz positive bursts (Fig. 1).⁴⁰ WS and RMTD are localized over the temporal lobe regions. For their identification, the three temporal electrodes of the 10–20 montage are needed. Midline theta rhythm and POSTs also require appropriate electrodes — vertex and occipital electrodes — respectively. Finally, the physician’s expertise in their recognition is essential.³

Given the limitations of the current literature about BEVs, a prospective observational study was carried out over a period of 9.5 years. All patients included in this study underwent continuous video-EEG monitoring for at least 24 hours using the 10–20 system and a lower temporal line systematically (Fig. 1). The goal was to investigate the prevalence of each type of BEV and its distribution according to the sleep–wake cycle.

during wakefulness, NREM (14.1%, 1.3%, respectively) and REM sleep (3.3%, 1.1%, respectively). Mu rhythm was also observed during NREM (1.5%) and REM sleep (7.7%). Fourteen- and 6-Hz positive bursts were present during NREM (4.5%) and REM sleep (6.5%). BSSS and six-Hz SW bursts were only observed during NREM sleep.

Conclusions. — The prevalence of BEVs is much higher than current estimates. POSTs and WS can no longer be considered as unusual patterns but physiological patterns of NREM sleep. RMTD and mu rhythm may be observed during NREM and REM sleep.

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Table 1  Distribution of benign EEG variants (BEVs) in the wake/sleep stages among 1163 patients.

| BEVs                     | Frequency | % of the group with BEV | % of total (N = 1163) |
|--------------------------|-----------|-------------------------|-----------------------|
| POSTs                    | 423       |                         | 36.4                  |
| Mu rhythm                | 260       |                         | 22.4                  |
| Wakefulness              | 218       | 84                      | 18.7                  |
| NREM sleep               | 17        | 6.5                     | 1.5                   |
| REM sleep                | 89        | 34                      | 7.7                   |
| Lambda waves             | 194       |                         | 16.7                  |
| Wicket spikes            | 175       |                         | 15                    |
| Wakefulness              | 34        | 19                      | 2.9                   |
| NREM sleep               | 164       | 94                      | 14.1                  |
| REM sleep                | 38        | 22                      | 3.3                   |
| 14- and 6-Hz positive bursts | 97   |                         | 8.3                   |
| NREM sleep               | 52        | 54                      | 4.5                   |
| REM sleep                | 75        | 77                      | 6.5                   |
| BSSS                     | 38        |                         | 3.3                   |
| RMTD                     | 25        |                         | 2.15                  |
| Wakefulness              | 11        | 44                      | 0.9                   |
| NREM sleep               | 15        | 60                      | 1.3                   |
| REM sleep                | 13        | 52                      | 1.1                   |
| Midline theta rhythm     | 24        |                         | 2.1                   |
| Six-Hz SW                | 1         |                         | 0.1                   |

BEVs were present in 710 patients (61%). For an individual patient, BEVs can be present in different states of vigilance.

POSTs: positive occipital sharp transients of sleep; BSSS: benign sporadic sleep spikes; RMTD: rhythmic midtemporal theta bursts of drowsiness; six-Hz SW: six-Hz spike and wave bursts.

EEG analysis

The EEGs were analyzed by two board-certified neurophysiologists/epileptologists (A.C. or P.G.), and the results were only included in the database after joint validation.

Statistical analysis

Characteristics of the study population were presented using means and standard deviations (SD) and frequencies and proportions for categorical variables using median and range (or mean and SD) for continuous variables.

Results

During the study period, 1175 patients were recorded. Twelve of them have been excluded from the study because of incomplete clinical data or EEG recording. The studied population includes 1163 subjects with a mean age of 33.9 ± 16.3 years (range 1–84). There were 625 females (53.7%) and 538 males (46.3%). The mean duration of EEG monitoring was 45.11 ± 23.53 hours (range 24–192). There were 917 patients with a diagnosis of epilepsy (79%) and 246 non-epileptic patients (21%).

Out of 1163 patients, we identified 710 patients (61%) with BEVs, 418 (59%) females, and 292 (41%) males (sex ratio F/M 1.43), with a mean age of 33.88 ± 16.25 years. Among them, 352 had only one BEV (49.6%) in the same recording, while 224 (31.5%) had two different BEVs, 105 (14.8%) of subjects had three BEVs, and 29 (4%) of sub-
Figure 2  39-Year-old man with recurrent syncope. (A) At the beginning of the plate, background activity with alpha rhythm. The mu rhythm continues over the left central region after eyes opening. Note eyelid movement artifacts upon opening of eyes. (B) Same patient. NREM sleep stage 2 with rare low voltage POSTs. Mu rhythm at F3–C3 and C3–P3.
Figure 3 18-Year-old woman with confusional arousals. (A) Eyes open. Bilateral mu rhythm with predominance over the vertex region. The frequency is at 8 Hz. Interestingly, the topographic distribution is not limited to the central region. The activity spreads to the parietal regions. To test the reactivity of this mu rhythm, it would have been necessary to have the patient move her feet due to its localization near the vertex. (B) Same patient, eyes open. Midline theta waves can be observed in phase reversal under Fz. They spread to the left and right frontal regions. The frequency is around 6 Hz. These waveforms correspond to the midline theta rhythm. Note the differences between the mu rhythm at 8 Hz and the midline theta rhythm at 6 Hz.
Figure 4  42-Year-old woman with left temporal lobe epilepsy. REM sleep. Muscular twitches at the beginning of the plate. Mu rhythm over the right central region (A) and rhythmic mid-temporal theta burst of drowsiness over the right temporal region (B). The morphology is typical. Electrode artifact at F3.

Projects had four or more BEVs. The data are shown in Table 1.

More precisely, among the 1163 patients, POSTs were observed in 423 patients (36.4%); mu rhythm was present in 260 participants (22.4%) (Figs. 2–4); lambda waves were observed in 194 patients (16.7%); WS were present in 175 patients (15%); 14- and 6-Hz positive bursts were observed in 97 patients (8.3%) (Fig. 5); BSSS were present in 38 patients (3.3%); RMTD were observed in 25 patients (2.1%) (Fig. 4); midline theta rhythm was present in 24 patients (2.1%) (Fig. 3B); six-Hz spike and wave bursts were observed in one patient (0.1%). We did not identify any SREDA during the study period.

The distribution of BEVs, according to the sleep-wave cycle, was evaluated. For an individual patient, BEVs can be present in more than one state of vigilance. Mu rhythm was present in 218 participants in wakefulness (18.7% of total) (Figs. 2A and 3A), in 17 patients in NREM sleep (1.5%) (Fig. 2B), and 89 patients in REM sleep (7.7%) (Fig. 4), respectively 84%, 6.5%, and 34% of patients with mu rhythm. WS were observed in 34 patients in wakefulness (2.9% of total), in 164 patients in NREM sleep (14.1%), and 38 patients in REM sleep (3.3%), respectively 19%, 94%, and 22% of patients with WS. Fourteen- 6-Hz positive bursts were observed only in sleep: in 52 patients during NREM sleep (4.5% of total), and in 75 patients in REM sleep (6.5%) (Fig. 5), respectively 54% and 77% of subjects with 14- and 6-Hz positive bursts. RMTD was present in 11 patients in wakefulness (0.9% of total), in 15 patients in NREM sleep (1.3%), and 13 patients in REM sleep (1.1%) (Fig. 4), respectively 44%, 60% and 52% of patients with RMTD. We identified lambda waves and midline theta rhythm only in wakefulness. POSTs, and BSSS were only present in NREM sleep. Some examples of BEVs in the sleep–wake cycle are shown in the supplementary material.

In the study group, the most frequent BEV in wakefulness was mu rhythm (18.7%), followed by lambda waves (16.7%), wicket spikes (2.9%), midline theta rhythm (2.1%), and RMTD (0.9%). In NREM sleep, POSTs were the most frequent pattern (36.4%), followed by WS (14.1%), 14- and 6-Hz positive bursts (4.5%), BSSS (3.3%), mu rhythm (1.5%), and six-Hz spike and wave bursts (0.1%). In REM sleep the most frequent pattern was mu rhythm (7.7%), then 14- and 6-Hz positive bursts (6.5%), WS (3.3%), and RMTD (1.1%).

Discussion

In the present study, the BEV prevalence was higher than previously reported (Table 2). Significant methodological differences explain this discrepancy, the first of which is...
Figure 5  (A) 5-Year-old boy with a history of febrile seizures. The child is in REM sleep. A 14- and 6-Hz positive burst can be observed over the left temporal region, especially on T1–T5. (B) 18-Year-old woman with genetic (idiopathic) generalized epilepsy. REM sleep, 14- and 6-Hz positive bursts can be observed. Note the presence of the fast variant at the beginning of the first burst, followed by the slow variant.
the EEG recording duration with a sufficient amount of both NREM and REM sleep. Radhakrishnan et al. (1999) investigated 1778 patients who underwent a sleep deprivation EEG recording.31 Eighty-two percent of the subjects were studied for epileptic seizures. Santoshkumar et al. (2009) evaluated the prevalence of BEVs in 35,249 subjects who underwent a standard EEG recording, but spontaneous sleep or drowsiness was obtained in the majority of cases.33 Indications were seizure disorders, stroke, encephalitis, psychological or behavioral symptoms, metabolic encephalopathy, dementia, blackouts, headaches, and dizziness.

The prevalence of WS was 15% in our study, which is considerably higher than previously reported (Table 2). A similarly high prevalence (10%) was found in a group of 479 subjects who underwent long-term EEG recording (1–6 days).42 The authors postulated a higher likelihood of detecting WS if a long-term, rather than a standard EEG was done. WS are usually seen during drowsiness and light NREM sleep, but they may also occur during wakefulness, even though it is more difficult to recognize them. During wakefulness, WS are often irregular with a theta-like morphology.3 Sleep recordings are particularly interesting to confirm WS (see supplementary material for an example). In our cohort, the prevalence of WS in wakefulness was less than 3%, while in NREM sleep, it increased to 14%. WS disappear during deep sleep but can reappear in REM sleep with a slightly lower amplitude,14 or in rare cases, exclusively present in REM sleep.25 In REM sleep, our prevalence was more than 3%, which confirms the importance of a full night’s sleep recording, with REM and NREM phases.

The prevalence of RMTD with a full-night sleep period was 2.15%. Maulsby et al. (1968) reported a figure similar,33 but more recent studies, with a shorter period of sleep, reported a lower prevalence (0.122%–0.79%) (Table 2).31,33 This activity is mostly seen during drowsiness and ceases during deeper sleep. However, in our study, the activity persisted during NREM sleep (1.3%) and above all, during REM sleep (1.1%) (Fig. 4). The former name “Rhythmic Mid-Temporal Discharges” proposed by Lipman and Hughes (1969) seems more appropriate.13 BSSS are low voltage diphasic spikes that occur singly and predominantly over the anterior or mid-temporal regions. During normal nocturnal sleep, we found a prevalence of about 3%, a medium value between those previously reported: 1.85% in Santoshkumar et al. (2009),21 8.16% in Radhakrishnan et al. (1999),21 and 11% in Jabbari et al. (2000).18 In these last two studies, the authors evaluated the EEG after sleep deprivation,18,31 which has been shown to facilitate the appearance of BSSS.26

The prevalence of 14- and 6-Hz positive bursts of more than 8% was still higher than in previous reports (0.5%–5.68%) (Table 2).31,33 These bursts are not present in wakefulness and are observed in NREM sleep. Older studies reported their presence in REM sleep.10,37,39 We found a higher prevalence of 14- and 6-Hz positive bursts during REM sleep than NREM sleep (6.5% vs. 4.5%, respectively). Their identification depends mainly on the recording techniques used and the length of the sleep portion. The long-distance or referential montages to the contralateral ear were recommended,33 but as mentioned in the introduction, the application of a lower temporal line increases the detection of the 14- and 6-Hz positive bursts.40 They had the highest amplitude over the temporal leads, especially with the bipolar derivations T2–T6 and T1–T5 (Fig. 5). REM sleep is classically identified by rapid eye movements and sawtooth waves. Based on our experience, REM sleep can be identified by the presence of 14- and 6-Hz bursts. They may be present only in this stage from the onset or may be present in NREM sleep but with a clear activation in REM sleep. These bursts are mainly seen in younger people, as we previously reported (prevalence of 62% in patients aged 15–25 years).40

Mu rhythm was first described in detail by Gastaut et al. (1952).8 Also labeled somatosensory alpha rhythm, this rhythm occurs unilaterally or bilaterally over the vertex, central or centro-parietal regions during wakefulness (Figs 2 and 3). Mu rhythm can be detected as early as infancy9 and has been reported to occur in about 10% of the population (from 2.9% to 18%).9,10,34 Our prevalence of 22.4% is considerably higher. Its presence during sleep confirms the results of older studies. In a study conducted on 20 subjects, mu rhythm was found in stage I (17 subjects), stage II (4 subjects), transitions from stage II-I (4 subjects), and REM sleep (2 subjects).44 It was notably similar during both the wakefulness and sleep stages. More recently, six cases have been
described with mu rhythm in REM sleep. Mu rhythm is easy to identify in REM sleep. It is more difficult in NREM sleep; confusion with normal sleep spindles is possible. Despite these difficulties, in our study, mu rhythm was recorded during NREM sleep in 1.5% of cases, compared to 7.7% in REM sleep (Figs. 2B and 4).

Six-Hz spike-and-wave bursts (phantom spike-and-wave bursts) are ambiguous patterns. These bursts appear to be more often associated with epilepsy when they predominate over the anterior regions rather than the posterior regions. Two types may be differentiated by considering the topography, gender, and pathological significance of the bursts. FOLDs (female occipital predominant low amplitude and Drowsiness) correspond to the benign variant, whereas WHAMs (wake high amplitude anterior predominance in Males) are more often associated with epilepsy. Even if we systematically use this categorization, the distinction between BEVs or epileptiform anomalies was highly suggestive. How these graphoelements are interpreted depends on the clinical context: in non-epileptic patients, it would be considered a BEV, but on the other hand, in genetic (idiopathic) generalized epileptic patients, this pattern is often considered a marker of the epileptic syndrome. Our prevalence of less than 0.1% (1 case) is considerably lower than previous studies (Table 2) but reflects the difficulties when it comes to their pathological significance. In our tertiary center for epilepsy, we tend to more often consider this pattern as a marker of epilepsy rather than a BEV. Classically, this pattern usually occurs bilaterally and synchronously during relaxed wakefulness, drowsiness, or light sleep and tends to disappear during deeper sleep stages. We reported one case that corresponds to the FOLDs pattern, in which six-Hz spike-and-wave bursts reappeared in REM sleep.

POSTs are seen, either symmetrically or not, over the occipital areas. POSTs occur in adolescents and young adults, and their prevalence falls over the age of 70. A full montage EEG with occipital electrodes is necessary to detect POSTs. POSTs occur in stage N2, and they may persist in stage N3 but disappear during REM sleep. The prevalence of POSTs varies widely from one study to another, depending on the type of EEG recording. Our prevalence of more than one-third of the patients shows that POSTs cannot be considered an unusual pattern but a physiological pattern of NREM sleep. POSTs are sometimes called lambdoid waves of sleep because of their similarities with the lambda waves, of course, only observed during wakefulness. Lambda waves’ prevalence of more than 16% is higher than studies with routine EEG. These waves occur when individuals are visually scanning a picture in a well-illuminated room. During long-term video-EEGs, patients read and watch television. Alvarez et al. (2011) found a prevalence of 1.7% for lambda waves in 2072 standard EEG reports versus 32.2% in 143 prolonged EEG monitoring reports. Lambda waves are easily recognizable, but it is difficult to estimate the exact prevalence. Their presence is dependent on the activity of the patients and/or the condition of the recording, which can vary considerably from one EEG laboratory to another. Lambda waves are not present when the room is not as bright.

Midline theta rhythm was first described by Cigánek (1961) as an EEG pattern of temporal lobe epilepsy. Studies that followed demonstrated its presence in normal subjects during drowsiness or wakefulness, especially during mental tasks. This unusual sinusoidal activity occurs predominantly over the vertex (Cz) (Fig. 3B), so reduced montages without midline electrodes fail to detect it. Here again, the probability of seeing this activity depends on the duration of the EEG recording. Our result of 2.1% is in line with a study conducted by the team of Cigánek (1971). They evaluated 1100 patients and found midline theta rhythm in 23 cases (2.09%). The presence of this rhythm also depends on the age of the patients. Westmoreland and Klass (1986) found 60% of midline theta rhythm in the age group of 10–40 years. More precisely, Okada and Urakami (1993) reported that midline theta rhythms were difficult to observe under 20 years of age; 45.7% of the patients were between 21 to 40, and 28.6% were over 61 years of age.

In conclusion, this study was specifically conducted on a population submitted to long-term video-EEG monitoring for at least 24 hours to evaluate the prevalence of BEVs and their correlation with the different stages of wakefulness and sleep. The identification of BEVs depends mainly on recording techniques used, the length of the sleep portion, as well as the experience of the team. We found a higher prevalence of WS, RMTD, and 6–14 Hz positive bursts than previously reported. POSTs and WS must now be considered as physiological patterns of NREM sleep. We confirm in a large case series that mu rhythm may be present in sleep, especially during REM sleep.

Conflict of interest

The authors report no conflicts of interest relevant to this article.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.neuci.2021.03.006.

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