A Special Electroencephalography Pattern Might Help in the Diagnosis of Antibody-positive Encephalitis

Li-Ping Mei¹, Li-Ping Li², Jing Ye¹, Yu-Ping Wang³, Jun Zhao¹, Tong Zhang¹

¹Department of Neurology, China Rehabilitation Research Center, Beijing Bo’ai Hospital, Capital Medical University, Beijing 100068, China
²Department of Neurology, Beijing Xuanwu Hospital, Capital Medical University, Beijing 100053, China

Li-Ping Mei and Li-Ping Li contributed equally to this work.

Abstract

Background: Patterns observed with electroencephalography (EEG) for patients who have encephalitis are usually known as generalized nonspecific cerebral abnormalities. The aim of this study was to investigate the presence of a special EEG pattern for patients with encephalitis and to explore features related to this special and uncommon pattern.

Methods: EEG monitoring was performed for every patient aged >15 years with encephalitis who was hospitalized between December 2011 and March 2014. Clinical characteristics and EEG recordings were collected and evaluated.

Results: Fifty-two patients with encephalitis were enrolled in our study with a 2-h median EEG recording time, and extreme beta brushes (EBBs) occurred in 17 patients (32.7%). Its presence was not significant regarding gender, age, psychiatric medication use, EEG rhythmic disorganization (P > 0.05). Nevertheless, among the patients with EBBs, nine patients (52.9%) had epileptic seizures that had a significant detection rate (P < 0.05); moreover, the cerebrospinal fluid (CSF) or serum of 15 patients (88.2%) with EBBs was positive for antibodies (P < 0.05). Four patients (23.5%) who had EBB had corresponding regional distributions on neuroimaging scans. The EBBs completely correlated with the regional distributions of spike discharges for four patients.

Conclusion: EBB is a special EEG pattern for patients with encephalitis, especially those with epileptic seizures or who have antibody-positive CSF/serum, and should be considered in clinical practice.

Key words: Antibodies; Electroencephalography; Encephalitis

Introduction

Encephalitis is a brain disorder manifesting with headaches, fever, altered consciousness, cognitive impairment, seizures, or even psychiatric symptoms. Patterns observed with electroencephalography (EEG) for patients who have encephalitis are usually known as generalized nonspecific cerebral abnormalities including background slowing, rhythmic slow-wave activity (theta or delta activity), or spike discharges.¹⁻⁶ However, one study showed that extreme delta brushes (beta frequency activity of 20–30 Hz riding on rhythmic delta frequency activity of 1–3 Hz) were a novel and abnormal EEG pattern that appeared in 30.4% of patients with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis.⁷ Thus far, the specificity of this pattern has not yet been determined. Additionally, whether other variations exist is unclear; an obvious beta frequency activity of 20–30 Hz overlapping above a rhythmic theta frequency of 4–7 Hz in EEG traces of patients with encephalitis. Thus, we defined this special EEG pattern as extreme beta brush (EBB), which comprised bursts of a faster, low-amplitude beta (20–30 Hz) frequency range that was superimposed on moderate-amplitude theta (4–7 Hz) or delta (1–3 Hz) frequency waves. This study investigated the presence of EBB (EBB: Beta activity overlapping above theta or delta activity) in 52 patients with encephalitis and explored the relationship between EBBs and encephalitis.

Address for correspondence: Dr. Li-Ping Li,
Department of Neurology, Beijing Xuanwu Hospital,
Capital Medical University, Beijing 100053, China
E-Mail: dr_lipingxw@163.com

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Methods

Patients
All hospitalized patients with encephalitis who were older than 15 years with serum or cerebrospinal fluid (CSF) positive for encephalitis that was diagnosed by neurologists were retrospectively enrolled. The patients underwent EEG monitoring between December 2011 and March 2014. Patients’ gender, age, date of onset, exacerbation of encephalitis, psychiatric medication use, epileptic seizures, neuroimaging findings, and times and duration of EEG monitoring were obtained. The cases were distinguished according to the etiology of their encephalitis from either serum or CSF results.

The study was approved by the Ethics Committee at our hospital.

Electroencephalography
The EEG recording comprised 28 electrodes (Fp1, Fp2, Fpz, F8, F4, Fz, F3, F7, T4, C4, Cz, C3, T5, T3, P4, Pz, P3, T5, O1, Oz, O2, G1, G2, PG1, PG2, A1, A2, and electrocardiogram) that were arranged according to the international 10–20 system. The sampling frequency was 256 Hz. The filtering frequency ranged from 0.5 Hz to 70 Hz. Sensitivity was set to 100 μV/cm. The EEG was interpreted by at least two experienced EEG readers. We evaluated basic EEG frequencies including background, abnormal slow-waves (delta or beta activity; generalized or focal), fast waves (beta activity), spike discharges, severity of EEG arrhythmia (mild, moderate, or severe), and EBBs. Considering variations, EBB was defined as low-amplitude bursts of rhythmic sharp beta waves of 20–30 Hz that were superimposed on low or moderate-amplitude delta waves of 1–4 Hz or theta waves of 4–7 Hz that could be rhythmic.

All patients underwent neuroimaging, magnetic resonance imaging (MRI) or computed tomography (CT), with a <5-day interval to the EEG. Correlation of significant EBB regions and neuroimaging abnormalities were studied.

Statistical analysis
Analyses were conducted on the measurement data using the Mann–Whitney U-test or independent t-test. Count data were compared using the Chi-square test between two groups of patients with and without EBBs. A Logistic regression model was utilized to evaluate possible influencing factors.

Results

Patient characteristics
Fifty-two patients with encephalitis were recruited, and 24 patients (46.2%) were male. The median age was 32.5 years (range, 15–77 years). All patients underwent neuroimaging examinations (49 patients [94.2%] for MRI and three patients [5.8%] for CT), and abnormalities were found in 30 patients (57.7%). Twenty-eight patients (53.8%) were diagnosed with antibody-positive encephalitis (including anti-NMDAR, anti-GABA<sub>a</sub>, anti-Lgi1, anti-CV2, and anti-Ro), whereas 24 patients (46.2%) had antibody-negative encephalitis (including autoimmune, viral, and bacterial encephalitis). Fifteen patients (28.8%) had epileptic seizures during or before hospitalization. Twenty-one patients (40.4%) were prescribed psychiatric medications because of personality or behavioral changes. The interval between EEG monitoring and acute encephalitis exacerbation ranged from 1 to 191 days (median, 18.5 days). The EEG monitoring duration varied from 20 min to 50 h (median, 2 h).

Electroencephalography presence
The EEG tracings were abnormal for all 52 patients. The basic background frequency varied from 2 to 12 Hz (34 patients [65.4%] mostly had an alpha frequency range; 6 [11.5%] had a delta frequency range; and 12 [23.1%] had a theta frequency range) with some degrees of background dysfunction. Generalized and focal slowing was seen in 50 patients (96.2%). The occurrence rates of abnormal delta and theta frequency activity were found in 26 patients (50.0%) and 24 patients (46.2%), respectively. The obvious beta activity occurred in 28 patients (53.8%); a low-amplitude beta frequency of 21–30 Hz was the main pattern (89.3%). Only eight patients had EEG tracings (15.4%) that recorded spike discharges. The EEG recordings indicated a mild, moderate, or severe EEG rhythm disorder in 21 (40.4%), 22 (44.2%), or seven (13.5%) patients, respectively.

Extreme beta brushes
Of the 52 patients, 17 patients had EEG recordings (32.7%) that had EBBs. EBBs could appear while the patient was awake, asleep, or both and were commonly seen in focal regions [Figures 1 and 2]. In most cases, the EBBs were intermittently present. The locations of the lesions were as follows: 12 lesions (70.6%), frontal regions; 11 lesions (64.7%), temporal regions; 11 lesions (64.7%), central regions; seven lesions (41.2%), parietal regions; and three lesions (17.6%), occipital regions. The EBBs were hemispheric for one patient and global for one patient. Based on the EEG recordings, EBBs could not be evoked by either eye movements or hyperventilation.

Table 1 shows a summary of the clinical characteristics and EEG findings between the two groups of patients with

![Figure 1: Central- and parietal-oriented rhythmic 30-Hz beta frequency activity is superimposed on polymorphic delta frequency waves of 2–4 Hz on a bipolar montage (1 s; 100 μV/cm).](image-url)
and without EBBs. By comparison, EBB presence was not significant regarding gender, abnormality observed in neuroimaging scans or psychiatric medications. Nevertheless, EBBs tended to exist in the EEG recordings of patients with encephalitis who were younger ($P < 0.05$), had epileptic seizures ($P < 0.05$), and had positive antibodies ($P < 0.05$). However, EBB presence was only influenced by epileptic seizures ($P < 0.05$) and positive antibody presence ($P < 0.05$) using a Logistic regression model.

As for etiology, detection rates for EBBs were 54.5% for anti-NMDAR encephalitis, 50.0% for other antibody-positive encephalitis, and 8.3% for antibody-negative encephalitis (16.7% for nonanti-NMDAR encephalitis). The results indicated that the EBB pattern was nonspecific for encephalitis. Among 17 patients with EBBs, 15 were antibody-positive, including 12 with anti-NMDAR encephalitis, one with anti-GABA$_\text{A}$, one with anti-Ro, and one with anti-Lgi1 encephalitis. Moreover, there was no significant difference in detection rates for EBBs between anti-NMDAR (54.5%) and other antibody-positive (50.0%) encephalitis ($P > 0.05$). For two patients with antibody-negative encephalitis, EBBs also appeared in their EEG recordings. The results showed that the detection rates for EBBs were higher in the EEG recordings from anti-NMDAR encephalitis patients (54.5%) than those with others (16.7%) that were significant ($P = 0.004$). The study indicated interval differences regarding exacerbation, times, EEG monitoring duration, basic frequency, presence of slow-waves and beta waves, spike discharges, and severity of EEG arrhythmia between patients with and without EBBs, but this study indicated no significance ($P > 0.05$).

**Extreme beta brush, neuroimaging findings, and spike discharges**

Of 17 patients with EBBs, only seven patients had neuroimaging findings (58.8%) that were abnormal. The EBBs coincided with abnormalities on neuroimaging, including distributed regions for four patients (23.5%) and by distributed sides for five patients (29.4%). The EBBs and regional distributions of spike discharges had complete correlation for four patients.

**DISCUSSION**

We observed “brushes of two patterns” or mixtures of beta and delta or theta frequency waves in 17 patients with encephalitis out of a total of 52 patients, especially in patients with antibody-positive encephalitis that was seen in previous studies.$^{[7,8]}$ We defined this special EEG pattern as EBB. The typical EBB pattern comprised bursts of faster, low-amplitude beta (20–30 Hz) frequency range that was continuously superimposed on generalized, rhythmic, and moderate-amplitude delta (1–3 Hz) frequency waves that were synchronous and symmetric. However, our study showed that the EBB pattern was commonly seen sporadically or paroxysmally in the focal regions, usually nonsynchronously and nonsymmetrically.

In this study, we found that patients with positive antibodies in their CSF or serum were more likely to have EBBs in their EEG tracings ($P < 0.05$). In addition, of the 17 patients with

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**Table 1: EEG changes between the two groups with and without EBBs**

| Indices                              | Without EBBs ($n = 35$) | With EBBs ($n = 17$) | All ($n = 52$) | $P$  |
|--------------------------------------|-------------------------|----------------------|---------------|------|
| Gender (n, %)                        |                         |                      |               |      |
| Male                                 | 16 (45.7)               | 8 (47.1)             | 24 (9.027)    |      |
| Female                               | 19 (54.3)               | 9 (52.9)             | 28            |      |
| Age (y)                              | 42.4 ± 18.9             | 28.6 ± 10.9          | 52 (0.022)    |      |
| Epileptic seizures (n, %)            | 6 (17.1)                | 9 (52.9)             | 15 (0.02)     |      |
| Psychiatric medication (n, %)        | 11 (31.4)               | 10 (58.8)            | 21 (0.059)    |      |
| Etiology (n, %)                      |                         |                      |               |      |
| Negative antibody                    | 22 (62.9)               | 2 (11.8)             | 24 (0.001)    |      |
| Positive antibody                    | 13 (37.1)               | 15 (88.2)            | 28            |      |
| NMDAR                                | 10 (76.9)               | 12 (80.0)            | 22 (0.843)    |      |
| Non-NMDAR                            | 3 (23.1)                | 3 (20.0)             | 6             |      |
| Abnormal neuroimaging (n, %)         | 23 (65.7)               | 7 (41.2)             | 30 (0.093)    |      |
| EEG monitoring                       |                         |                      |               |      |
| Intervals with exacerbation (days)    | 31.5 ± 40.9             | 40.8 ± 53.8          | 52 (0.489)    |      |
| Times                                | 1.4 ± 0.7               | 1.5 ± 0.9            | 52 (0.482)    |      |
| Duration (h), median (range)         | 2 (0–5)                 | 2 (0.3–48)           | 52 (0.229)    |      |
| Basic frequency (Hz)                 | 7.8 ± 2.2               | 7.5 ± 3.0            | 52 (0.690)    |      |
| Slow-waves (n, %)                    | 34 (97.1)               | 16 (94.1)            | 50 (0.595)    |      |
| Delta activity                       | 20 (58.8)               | 6 (37.5)             | 26 (0.159)    |      |
| Theta activity                       | 14 (41.2)               | 10 (62.5)            | 24            |      |
| Beta waves (n, %)                    | 16 (45.7)               | 12 (70.6)            | 28 (0.091)    |      |
| 14–19 Hz                             | 2 (12.5)                | 1 (8.3)              | 3             | 0.724|
| 20–30 Hz                             | 14 (87.5)               | 11 (81.7)            | 25            |      |
| Spike waves (n, %)                   | 4 (11.4)                | 4 (23.5)             | 8             | 0.413|

EEG: Electroencephalography; NMDAR: N-methyl-d-aspartate receptor; EBB: Extreme beta brush.
an EBB pattern, 28.8% of the patients had epileptic seizures, but only 15.4% of the patients’ EEG tracings recorded spike discharges. The results demonstrated that the appearance of EBBs was associated with epileptic seizures \((P < 0.05)\), rather than spike discharges \((P > 0.05)\), and a reason might be because EBBs appeared more easily in patients with severe encephalitis who probably had epileptic seizures. It is well known that psychiatric medications might cause the appearance of fast waves on EEG tracings.\[9\] Our study showed that seven patients (41.2%) who had an EBB pattern were not prescribed oral or intravenous psychiatric or anti-epileptic medications; 11 patients (31.4%) who did not have EBBs were prescribed psychiatric or anti-epileptic medications. By conducting an analysis of the relationship between EBB presence and psychiatric medication use, we believe the EBB pattern is rarely associated with medication usage that is consistent with two other studies.\[7,8\]

From etiology, EBB detection rates for anti-NMDAR, other antibody-positive, and antibody-negative encephalitis were 54.5%, 50.0%, and 8.3%, respectively. Anti-NMDAR and other antibody-positive encephalitis groups were significantly higher than the antibody-negative encephalitis group \((P < 0.05)\). The EBB detection rates in anti-NMDAR encephalitis were much higher in our study than in another study.\[7\] The most likely explanation is that the studies utilized different definitions for “brushes” as previously noted; the definition provided in medical literature involves only beta and delta waves, while we included theta waves as well in our definition. Usually for EEG recordings, the longer the monitoring period is, the more likely an abnormality is present. Although EBBs were intermittently present, the results showed that the EBB detection rates were not associated with the duration of the EEG recordings that was inconsistent with our expectation. However, the results showed no association between the EEG recording duration and EBB presence that differed from findings of another study.\[7\] The reason might be that the duration of EEG recordings in our study was much shorter than that of Schmitt et al.\[7\]

In this study, more than half (58.8%) of the patients with an EBB pattern had normal neuroimaging findings; this finding indicates that the interpretation of EBB patterns could play an effective role in the diagnosis of encephalitis, especially for antibody-positive encephalitis, as an EEG is a noninvasive examination. However, EBBs and neuroimaging examinations could not be completely correlated, which might be because the EEGs and neuroimaging examinations were not performed on the same day.

Because our study was retrospective, rather than prospective, the information that we gathered was insufficient; we did not consider the severity and prognosis of patients’ conditions. Further, whether EBB patterns occur in the EEG recordings of other encephalopathies is unclear. In addition, the number of antibody-positive cases was relatively small in our study, so the statistical power decreased. Moreover, the association between the EEG recording duration and EBB detection rates necessitate confirmation in additional prospective studies.

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Conflicts of interest
There are no conflicts of interest.

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