Clinical and imaging correlates of EEG patterns in hospitalized patients with encephalopathy

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Abstract To identify the relationship between pathologic electroencephalographic (EEG) patterns, clinical and neuroradiological abnormalities, and outcome in hospitalized patients with acute encephalopathy. This 5-year cohort study was performed at an academic tertiary care center. EEGs in 154 patients with altered mental status were classified according to five predefined patterns: Isolated continuous slowing of background activity (theta, theta/delta, and delta activity) and patterns with slowing background activity with episodic transients [i.e., triphasic waves (TWs) or frontal intermittent delta activity (FIRDA)]. Clinical characteristics, blood tests and neuroimaging were compared among groups. Associations between EEG patterns and structural and non-structural abnormalities were calculated. Glasgow Outcome Score >3 at discharge was defined as favorable and 1–3 as unfavorable outcome. In multivariable analyses, theta was associated with brain atrophy (OR 2.6, \( p = 0.020 \)), theta/delta with intracerebral hemorrhages (OR 6.8, \( p = 0.005 \)), FIRDA with past cerebrovascular accidents (OR 2.7, \( p = 0.004 \)), TWs with liver or multi-organ failure (OR 6, \( p = 0.004 \); OR 4, \( p = 0.039 \)), and delta activity with alcohol/drug abuse with or without intoxication, and HIV infection (OR 3.8, \( p = 0.003 \); OR 9, \( p = 0.004 \)). TWs were associated with death (OR 4.5, \( p = 0.005 \)); theta/delta with unfavorable outcomes (OR 4.5, \( p = 0.005 \)), while patients with FIRDA had favorable outcomes (OR 4.8, \( p = 0.004 \)). In encephalopathic patients, well-defined EEG patterns are associated with specific pathological conditions and outcomes, suggesting that mechanistic hypotheses underlie these abnormal EEG patterns. To clarify the respective contributions of non-structural and structural abnormalities to encephalopathy reflected in specific EEG patterns, prospective studies using continuous EEG monitoring during the acute onset of encephalopathy are needed.

Keywords Encephalopathy · EEG patterns · Triphasic waves · FIRDA · Theta activity · Theta/delta activity · Delta activity

Introduction

The acute onset of encephalopathy is frequent in hospitalized patients and has been associated with adverse outcome [13, 14]. The EEG in acute encephalopathy generally reveals a non-epileptiform disturbance such as slowing of
established or evolving dementia. The disturbance had to be

disturbance) or the development of a perceptual distur-

bance that was not better accounted for by a preexisting,

cognition (i.e., memory deficit, disorientation, language

was defined as altered consciousness and/or change in

Psychiatric Association, acute alteration in mental status

Based on the Diagnostic and

Statistical Manual of Mental Disorders of the American

February 2012 who underwent EEG to evaluate an acute

We identified hospitalized patients from October 2007 to

Design and setting

This observational cohort study was performed in the

Department of Neurology, Johns Hopkins Bayview Medi-

cal Center in Baltimore, USA. The study was approved by

the institutional review board (ethics committee) and has

requires imaging obtained during the same hospital stay, were

patients with alpha or spindle coma, and patients without

 EEGs were classified by two certified electroencephalog-

raphers into isolated continuous slowing of background

activity (theta, theta/delta, or delta activity) and patterns

with slowing background activity with episodic transients

(TWs or FIRDA). Theta activity was defined as generalized

slow background activity with a frequency of 4–7 Hz and

amplitudes of >40 µV without intrusions of delta (<4 Hz)

or alpha activity (8–13 Hz) for >20 % of recording during

wakefulness (Fig. 1a). Theta/delta activity was defined as

generalized slow background activity of 4–7 Hz and

amplitudes of >80 µV with intrusion of alpha activity

(8–13 Hz) for <20 % and intermixed with delta activity

(<4 Hz) in 20–50 % of recording during drowsiness or

arousal (Fig. 1b). Delta activity was defined as generalized

background activity of <4 Hz and amplitudes of >80 µV

with intrusion of theta or alpha activity for <20 % of

recording during drowsiness or arousal (Fig. 1c).

TWs were defined as repetitive electrographic elements con-

sisting of three phases, each longer than the preceding one:

a surface positive high-amplitude (>70 µV) wave preceded

and followed by negative waves with smaller amplitude as

first described 1950 [18] and precisely defined by Fisch

[17] (Fig. 1d). FIRDA was defined as a repetitive appear-

ance of rhythmic slow waves with a frequency <4 Hz with

a frontal predilection [1, 8, 10, 11, 22] (Fig. 1e). None of

the patients had TWs and FIRDA simultaneously. In

patients with TWs or FIRDA, slowing of background

activity was assessed as mentioned above. Patients with a

normal EEG were excluded. EEG with epileptiform dis-

charges, focal slowing, burst-suppression, flat-line EEG,

patients with alpha or spindle coma, and patients without

brain imaging obtained during the same hospital stay, were

excluded (N = 22).

Medical records were reviewed to extract demographic

information, hospital admission diagnosis, comorbidities,

highest and lowest Glasgow Coma Scale (GCS) on the day

day of EEG, critical illnesses, and critical interventions includ-

ing hemodialysis, mechanical ventilation and cardiopul-

monary resuscitation, administration of intravenous sedative

or anesthetic drugs during or 24 h prior to EEG, results from

chest X-rays, white blood cell counts, levels of blood glu-

cose, urea, ammonia, and urinanalysis on the day of EEG.

According to Cockcroft et al., renal insufficiency was

defined as a reduced glomerular filtration rate below 90 mL/

min [9]. Acute liver insufficiency was defined in accordance

with the American Association for the Study of Liver

Disease as a rapid development of liver injury with impaired

hepatic function and encephalopathy in a patient who pre-

viously had a normal liver or had well-compensated liver

disease [31]. Acute lung injury and acute respiratory distress

syndrome (ARDS) were defined as proposed by the ARDS

Network [36] and the Report of the American-European
Consensus Conference on ARDS [5]. Sepsis was assessed as defined by the International Sepsis Definitions Conference of 2001 [27, 28]. Septic shock was diagnosed when vasopressors were used for more than 1 h during sepsis.

EEG recording and interpretation

EEGs were recorded over at least 20 min with superficial scalp electrodes placed according to the International 10–20-System. Patients were stimulated by verbal commands, opening of the eyes, and if still no arousals were registered, sternal rub and toe compression were applied. Arousals were defined according to standard criteria as an abrupt shift in frequency of background activity, lasting for 3 s or more that may have included theta, alpha and/or frequencies >16 Hz but no spindles [3]. All EEG recordings were analyzed by two certified neurologists trained and boarded in EEG interpretation. Review and

Fig. 1 Examples of the five different EEG patterns in encephalopathic patients: a generalized slow background activity of 4–7 Hz (theta); b generalized slow background activity of 4–7 Hz with intrusions of delta activity (theta/delta); c generalized delta background activity (delta); d repetitive intermittent electrographic elements consisting of three phases and a fronto-central or fronto-parietal predominance and a fronto-occipital or occipito-frontal time shift (triphasic waves); e repetitive intermittent rhythmic slow waves with a frequency of <4 Hz with a frontal predilection (FIRDA)
interpretation of EEG was accomplished in a manner blinded to clinical or radiologic information. Consensus on discordant interpretations was reached by critical review.

Neuroimaging

Neuroimaging studies were interpreted by two neuroradiologists and one neurologist. CTs were performed with soft tissue algorithm reconstructions as well as bone algorithm reconstructions. Brain MRIs were performed on a 1.5 T scanner with T1- and T2-weighted, fluid-attenuated inversion recovery, and diffusion-weighted sequences. Lesion or injury patterns were noted including edema, infarction, hemorrhage, and gadolinium enhancement, as well as intracerebral neoplasms. White matter changes were characterized as mild, moderate and marked by using the scoring system as proposed by Schmidt et al. [32]: mild for punctate, moderate for beginning confluent, and marked for confluent white matter hyperintensities. Brain atrophy was graded as mild, moderate and marked according to the Brain Atrophy and Lesion Index [6].

Categorical and continuous outcome variables

The principal outcome measure was the dichotomized Glasgow Outcome Score (GOS) at discharge, designated as unfavorable (GOS 1–3) and favorable (GOS > 3). Secondary outcome was discharge destination (home, acute rehabilitation, another hospital, or skilled nursing facility).

Statistics

Categorical variables were summarized as counts and proportions, continuous variables as means and standard deviations. Patients were categorized according to their EEG patterns. Comparisons of these five groups were performed as follows: Analysis of variance (ANOVA) for comparison of continuous variables and Pearson Chi-square test with Fisher’s exact test were appropriate for comparison of categorical variables. Significant findings in ANOVA global test were additionally evaluated by multiple comparison tests using Bonferroni corrections. Covariates were categorized as structural (i.e., brain abnormalities, such as atrophy, white matter changes, intracerebral hemorrhages, posterior reversible encephalopathy, past and present cerebrovascular accidents) and non-structural (i.e., organ failures or insufficiencies, infections, intoxications, or drug abuse). Univariable logistic regression was used to calculate the odds of patients’ clinical and imaging abnormalities having one of the five EEG patterns. For all significant results in the univariable logistic regression, a multivariable analysis was performed (adjusting for characteristics, which were significant in the overall comparisons and the use of intravenous anesthetic drugs, as evolution of cortical neuronal dysfunction by depth of anesthesia is well described [33]). Multiple logistic regression models were used for categorical outcomes and multiple linear regression models for continuous outcomes. As it was not the main aim of this study to identify independent associations of particular EEG patterns with different outcome variables, multivariable regression models were only adjusted for age. Adjustment for the use of intravenous sedative or anesthetic drugs was made for comparison of GCS on the day of EEG in the five patients groups. To assess collinearity, multiple linear regression was performed on all variables included in the multiple logistic regression analysis in order to calculate variance inflation factors. The mean variance inflation factor was 1.22, the highest value being 1.57 for age—all being below 2.0. Hosmer–Lemeshow goodness of fit tests were applied to check the final models. Levels for statistical significance were set at two-tailed p value of <0.05. Statistical analysis was performed with STATA® 12.0.

Results

Demographics and basic characteristics

154 patients met the inclusion and exclusion criteria. Mean age was 62.8 (±18) years with 43 % males and 57 % females. The mean of the lowest GCS on the day of EEG recording was 11 (±4). The majority of patients (70 %) were in the ICU including neurocritical care unit (38 %), medical intensive care unit (21 %), cardiac (10 %), and surgical care unit (2 %). All other patients were hospitalized on the neurological or medical wards. Only 13 % of patients received intravenous sedative or anesthetic drugs during or 24 h before EEG (11 had lorazepam, 6 midazolam, and 3 propofol) without significant differences between the five patients groups (p = 0.378). The most prevalent critical illness was renal insufficiency in 55 %, followed by respiratory failure (10 %), liver insufficiency (8 %), septic shock (6 %), and acute lung injury or acute respiratory distress syndrome (2 %). Cerebral CT was performed in 38 and 62 % of patients who received brain MRI. Mean time between EEG and neuroimaging was 2 (±15) days. Inter-rater agreement for neuroimaging interpretation was high (κ score 0.85) and all principal diagnoses were consistent with findings on brain imaging. Remarkably, 74 % patients showed brain atrophy (45 %) and/or white matter changes (66 %).

EEG patterns

The theta pattern was present in 22 % of patients, 21 % had theta/delta, 18 % delta, 22 % TWs, and 17 % presented...
with FIRDA. Of the 22 % with TWs, the majority had theta/delta background activity (68 %) followed by theta activity (32 %). The 17 % of patients with FIRDA mostly had theta background activity (73 %) and the remaining had theta/delta activity (27 %). In patients with FIRDA and dominant theta activity, 38 % had intrusions of alpha activity for >20 % of recording. Comparison of demographics and clinical characteristics between the five groups are presented in Table 1. Age was significantly different with patients having FIRDA and delta being younger. Mean of the lowest GCS on day of EEG for each patient group is shown in Fig. 2. Patients with theta/delta, delta or TWs had significantly lower GCS than those with FIRDA or theta (p < 0.0001).

The most common structural abnormalities were white matter changes (66 %), brain atrophy (45 %), followed by non-structural problems such as infections (47 %) and metabolic problems (58 %). All four of these medical conditions were detected in 15 % of patients, while three were present in 25 % and two in 31 %. Overall, 71 % of patients had two or more of these abnormalities.

Aside from the large numbers of co-occurring abnormalities, uni- and multivariable analysis for the associations of structural and non-structural abnormalities with the particular EEG patterns were performed (Table 2). Theta activity was significantly associated with brain atrophy and a diagnosis of dementia (OR 2.6, 95 % CI 1.16–5.66, p = 0.020; OR 2.7, 95 % CI 1.16–6.39, p = 0.0021, respectively); theta/delta pattern with intracranial hemorrhage (OR 6.8, 95 % CI 1.79–25.9, p = 0.005); FIRDA with prior cerebrovascular accidents (OR 2.7, 95 % CI 1.0–7.2, p = 0.004); and delta activity was linked to posterior reversible encephalopathy (OR 7.4, 95 % CI 1.18–46.8, p = 0.033). TWs were associated with liver insufficiency or multi-organ failure (OR 6, 95 % CI 1.76–20.2, p = 0.004; OR 4, 95 % CI 1.07–14.6, p = 0.039, respectively); delta activity with alcohol/drug abuse with or without intoxication (OR 3.8, 95 % CI 1.55–9.07, p = 0.003), as well as HIV-infection (OR 9, 95 % CI 1.99–39.9, p = 0.004). Of note, 42.9 % of HIV-infected patients had the diagnosis of HIV-encephalopathy, 75 % had signs of moderate to marked white matter changes, and 50 % had mild to moderate brain atrophy. The association of metabolic derangements with TWs is shown in Fig. 3. Multivariable analysis demonstrated that all associations remained significant, except for the one of posterior reversible encephalopathy with delta activity, indicating independent associations between these EEG patterns and structural and non-structural abnormalities.

Subgroup analysis for patients with only one isolated abnormality was not possible, as the numbers were too small. However, in six patients with only metabolic derangements, five had TWs.

Inter-rater agreement for EEG interpretation was good (k score 0.84) and consensus after additional review could be reached in all cases.

Course and outcome

Compared to patients with other EEG patterns, patients with a theta/delta pattern were more likely to require intensive care (OR 3.7, 95 % CI 1.2–11.2, p = 0.022), while patients with FIRDA needed ICU-treatment less frequently (OR 0.2, 95 % CI 0.1–0.6, p = 0.001).

Outcomes of patients in the five groups are presented in Table 3. Presence of a theta/delta pattern was associated with unfavorable outcome (OR 2.5, 95 % CI 1.08–5.98, p = 0.033). The presence of TWs was associated with high odds for death (OR 4.5, 95 % CI 1.57–12.7, p = 0.005). FIRDA was associated with favorable outcome (OR 4.8, 95 % CI 1.63–13.9, p = 0.004) and a high odds of being discharged home.

The Hosmer–Lemeshow goodness of fit test revealed insignificant p values for all multivariable logistic regression models, suggesting adequate model fit (range: p = 0.192–0.984).

Discussion

In this study of 154 hospitalized patients with encephalopathy, the most frequent medical conditions were the presence of white matter changes, brain atrophy, infections and metabolic problems. The majority (71 %) of patients had two or more of these abnormalities. We identified associations between the five well-defined EEG patterns and (1) selected structural and non-structural abnormalities, and (2) short-term outcome. A dominant theta pattern was independently linked with brain atrophy, theta/delta with intracranial hemorrhages, delta activity with alcohol/drug abuse and HIV-infection, and TWs with liver insufficiency or multi-organ failure, while FIRDA was associated with past cerebrovascular accidents. These associations remained significant in multivariable models and suggest mechanistic hypotheses underlying these abnormal EEG patterns. The magnitude of the OR estimates must be interpreted with caution, as the small sample size contributes to wide confidence intervals. The directions or relations of the identified associations did not change after adjustment for possible confounders. Our results indicate a clinical framework for interpreting several commonly described EEG abnormalities in patients with encephalopathy.

To our knowledge, significant associations of intracranial hemorrhage, posterior reversible encephalopathy, or HIV-infection with slow background activity has not previously been demonstrated. However, predominance of
| Demographics | Theta ($n = 34$) | Theta/delta ($n = 32$) | Delta ($n = 28$) | Triphasic waves ($n = 34$) | FIRDA ($n = 26$) | $p$ value$^a$ |
|--------------|-----------------|-------------------------|-----------------|--------------------------|------------------|---------------|
| Gender       |                 |                         |                 |                          |                  |               |
| Female       | 17 50           | 20 63                   | 12 43           | 23 68                    | 16 62            | 0.272         |
| Male         | 17 50           | 12 37                   | 16 57           | 11 32                    | 10 38            |               |
| Age (years)$^a$ | 67 ± 18     | 66 ± 13                 | 54 ± 19         | 68 ± 16                  | 57 ± 19          | 0.0024        |
| Clinical features |           |                         |                 |                          |                  |               |
| Principal diagnoses |       |                         |                 |                          |                  |               |
| Infections   | 19 56           | 18 56                   | 12 43           | 16 47                    | 7 27             | 0.203         |
| Respiratory tract infections | 3 9         | 11 34                   | 5 18            | 11 32                    | 5 19             | 0.068         |
| Urinary tract infections | 10 29     | 9 28                    | 3 11            | 1 21                     | 2 8              | 0.127         |
| Bacteremia   | 7 21            | 6 6                     | 6 21            | 3 9                      | 1 4              | 0.127         |
| Meningitis/Encephalitis | 1 3         | 2 6                     | 3 11            | 1 3                      | 1 4              | 0.324         |
| Endocarditis | 1 3             | 0 0                     | 0 0             | 0 0                      | 0 0              | 1.000         |
| Dementia     | 12 35           | 6 19                    | 4 14            | 0 0                      | 4 15             | 0.270         |
| Intracerebral hemorrhage | 1 3         | 6 19                    | 2 7             | 1 3                      | 0 0              | 0.036         |
| Subarachnoid hemorrhage | 2 6          | 2 6                     | 0 0             | 2 6                      | 1 4              | 0.781         |
| Subdural hemorrhage | 2 6          | 2 6                     | 0 0             | 1 3                      | 0 0              | 0.554         |
| Tumor (outside the CNS) | 3 9         | 6 19                    | 1 4             | 2 6                      | 4 15             | 0.279         |
| Brain tumor  | 2 6             | 4 13                    | 3 11            | 2 6                      | 1 4              | 0.740         |
| Acute ischemic stroke | 3 9           | 4 13                    | 2 7             | 2 6                      | 1 4              | 0.822         |
| Hydrocephalus | 1 3           | 3 9                     | 2 7             | 3 9                      | 1 4              | 0.804         |
| HIV-infection | 1 3           | 1 3                     | 5 18            | 1 3                      | 0 0              | 0.040         |
| Traumatic brain injury | 3 9           | 2 6                     | 1 4             | 1 3                      | 0 0              | 0.670         |
| Intoxication | 2 6             | 0 0                     | 3 11            | 0 0                      | 0 0              | 0.050         |
| Posterior reversible encephalopathy | 0 0      | 0 0                     | 3 11            | 1 3                      | 1 4              | 0.106         |
| Medication or drug withdrawal | 0 0      | 0 0                     | 0 0             | 1 3                      | 1 4              | 0.480         |
| Comorbidities |           |                         |                 |                          |                  |               |
| Arterial hypertension | 23 68  | 19 28                   | 20 71           | 24 71                    | 15 58            | 0.712         |
| Diabetes mellitus type 2 | 10 29    | 9 28                    | 9 32            | 13 38                    | 7 27             | 0.877         |
| Coronary artery disease | 8 24     | 7 22                    | 6 21            | 6 18                     | 3 12             | 0.806         |
| Known Epilepsy | 9 27      | 6 19                    | 2 7             | 3 9                      | 7 27             | 0.112         |
| Past cerebrovascular accident | 7 21    | 7 22                    | 2 7             | 2 6                      | 8 31             | 0.049         |
| Autoimmunodisease | 0 0      | 2 19                    | 1 4             | 0 0                      | 0 0              | 0.233         |
| Risk factors |                 |                         |                 |                          |                  |               |
| Smoking      | 6 18            | 10 31                   | 13 46           | 10 29                    | 12 46            | 0.086         |
| Atrial fibrillation | 5 15     | 9 28                    | 3 11            | 9 27                     | 2 8              | 0.152         |
| Alcohol abuse | 4 12        | 2 6                     | 8 29            | 5 15                     | 4 15             | 0.207         |
| Drug abuse   | 1 3             | 2 6                     | 7 25            | 5 15                     | 1 4              | 0.037         |
| Critical illness |           |                         |                 |                          |                  |               |
| Renal insufficiency | 19 56     | 22 69                   | 18 64           | 21 62                    | 5 19             | 0.001         |
| Respiratory failure | 3 9        | 6 19                    | 1 4             | 5 15                     | 1 4              | 0.248         |
| Liver insufficiency | 0 0       | 2 6                     | 3 11            | 7 21                     | 0 0              | 0.007         |
| Septic shock | 4 12           | 2 6                     | 0 0             | 3 9                      | 0 0              | 0.186         |
| ARDS or ALI | 4 12           | 0 0                     | 0 0             | 1 3                      | 1 4              | 0.782         |
| Additional findings on brain CT or MRI |         |                         |                 |                          |                  |               |
| White matter changes | 19 56     | 24 75                   | 20 71           | 24 71                    | 15 58            | 0.391         |
| Mild        | 4 12           | 6 19                    | 3 11            | 9 27                     | 6 23             | 0.414         |
delta activity in patients with alcohol/drug abuse or intoxication is consistent with early work on the neurophysiology of anesthetics [33]. Interestingly, there was no significant coincidence of patients with HIV infection and use of anesthetics or alcohol abuse that would have explained the prevalence of delta activity in patients with HIV. Encephalopathy related to HIV was diagnosed in nearly half of these patients. One possible explanation might be the high burden of marked confluent white matter changes (Schmidt’s score 3) seen in all our patients with documented HIV encephalopathy. Studies have described pronounced white matter changes in brain imaging of HIV-infected patients [21], possible correlates of the pathologic changes in the thalamo-cortical circuits that underlie cortical slowing. Overall there was a high prevalence of structural factors such as brain atrophy and/or white matter changes (74 %) in our cohort, suggesting diminished neurologic reserve. This contributes together with toxic, metabolic, and infectious elements to the appearance of encephalopathy. The co-occurrence of the most common structural with non-structural problems such as infections and metabolic problems was seen in up to one-third of our patients, underscoring the importance of their interplay in the genesis of encephalopathy. However, information on additional pathologic conditions, such as acute changes of blood flow or intracranial pressure could not be assessed retrospectively and would perhaps lead to an even larger proportion of patients with co-occurring acute and chronic pathologic conditions. Prospective studies are needed to determine particular EEG changes in these acute medical conditions and to answer the question if EEG might provide early information in the setting of such critical conditions.

The associations of specific EEG patterns with structural and non-structural pathologic conditions have been previously described with TWs and FIRDA [1, 10, 11, 15, 16, 19, 22, 24, 26, 30, 34, 35, 37]. TWs are thought to reflect the activity of thalamo-cortical circuits which also underlie generalized epileptiform discharges and the sleep spindle activity. These structures may well be modified by subcortical white matter disease caused by neurodegenerative or ischemic processes [26, 30, 34], leading to projected slow activity or the generation of non-epileptic periodic discharges or TWs [25]. However, in our study five of six patients with TWs had isolated metabolic problems with no signs of brain atrophy or white matter changes. This suggests that structural abnormalities may promote or enable projected slower activity (delta activity or TWs), but are not essential for their appearance [25]. A clear and isolated association of renal insufficiency with the appearance of
| Abnormalities/EEG patterns                | Crude OR (95% CI) | p value | Adjusted OR (95% CI) | p value |
|------------------------------------------|-------------------|---------|----------------------|---------|
| Brain atrophy                            |                   |         |                      |         |
| Theta                                    | 2.8 (1.29–6.29)   | 0.010   | 2.8 (1.29–6.29)      | 0.010   |
| Theta/delta                              | 0.9 (0.39–1.88)   | 0.702   |                      |         |
| Delta                                    | 0.7 (0.30–1.59)   | 0.383   |                      |         |
| Triphasic waves                          | 1.0 (0.47–2.18)   | 0.968   |                      |         |
| FIRDA                                    | 0.5 (0.23–1.32)   | 0.178   |                      |         |
| Intracerebral hemorrhage                 |                   |         |                      |         |
| Theta                                    | 0.4 (0.05–3.06)   | 0.359   |                      |         |
| Theta/delta                              | 6.8 (1.79–25.9)   | 0.005   | 7.4 (1.64–33.3)      | 0.009   |
| Delta                                    | 1.1 (0.23–5.66)   | 0.878   |                      |         |
| Triphasic waves                          | 0.4 (0.05–3.06)   | 0.359   |                      |         |
| FIRDA                                    | –                 |         |                      |         |
| Past cerebrovascular accident            |                   |         |                      |         |
| Theta                                    | 1.4 (0.53–3.62)   | 0.515   |                      |         |
| Theta/delta                              | 1.5 (0.57–4.01)   | 0.399   |                      |         |
| Delta                                    | 0.3 (0.07–1.47)   | 0.145   |                      |         |
| Triphasic waves                          | 0.3 (0.06–1.12)   | 0.070   |                      |         |
| FIRDA                                    | 2.7 (1.03–7.17)   | 0.004   | 3.6 (1.13–11.2)      | 0.030   |
| Posterior reversible encephalopathy      |                   |         |                      |         |
| Theta                                    | –                 |         |                      |         |
| Theta/delta                              | –                 |         |                      |         |
| Delta                                    | 7.4 (1.18–46.8)   | 0.033   | 4.9 (0.65–37.1)      | 0.124   |
| Triphasic waves                          | 0.9 (0.09–8.13)   | 0.909   |                      |         |
| FIRDA                                    | 1.2 (0.13–11.6)   | 0.850   |                      |         |
| HIV-infection                            |                   |         |                      |         |
| Theta                                    | 0.5 (0.06–4.12)   | 0.511   |                      |         |
| Theta/delta                              | 0.5 (0.06–4.47)   | 0.559   |                      |         |
| Delta                                    | 8.9 (1.99–39.9)   | 0.004   | 6.4 (1.18–35.2)      | 0.032   |
| Triphasic waves                          | 0.5 (0.06–4.12)   | 0.511   |                      |         |
| FIRDA                                    | –                 |         |                      |         |
| Alcohol abuse, drug abuse, or Intoxication|                 |         |                      |         |
| Theta                                    | 0.7 (0.28–1.97)   | 0.544   |                      |         |
| Theta/delta                              | 0.3 (0.09–1.12)   | 0.074   |                      |         |
| Delta                                    | 3.8 (1.55–9.07)   | 0.003   | 2.7 (1.03–7.13)      | 0.043   |
| Triphasic waves                          | 1.2 (0.47–2.89)   | 0.735   |                      |         |
| FIRDA                                    | 0.6 (0.20–1.95)   | 0.413   |                      |         |
| Renal insufficiency                      |                   |         |                      |         |
| Theta                                    | 1.0 (0.48–2.23)   | 0.927   |                      |         |
| Theta/delta                              | 2.1 (0.90–4.71)   | 0.087   |                      |         |
| Delta                                    | 1.6 (0.68–3.70)   | 0.287   |                      |         |
| Triphasic waves                          | 1.4 (0.65–3.08)   | 0.384   |                      |         |
| FIRDA                                    | 0.1 (0.05–0.40)   | <0.0001 | 0.2 (0.05–0.51)      | 0.002   |
| Liver insufficiency                      |                   |         |                      |         |
| Theta                                    | –                 |         |                      |         |
| Theta/delta                              | 0.7 (0.15–3.59)   | 0.715   |                      |         |
| Delta                                    | 1.6 (0.16–0.36)   | 0.527   |                      |         |
| Triphasic waves                          | 6.0 (1.76–20.2)   | 0.004   | 11.3 (2.11–60.5)     | 0.005   |
TWs could not be shown, possibly due to the small number of patients without renal problems. Aside from the significant association of liver insufficiency and multi-organ failure with TWs, there was a high odds ratio for TWs with every unit increase in ammonia or urea. Hughes et al. [23] have shown that patients with abnormal EEG patterns (defined as slow wave activity and/or epileptiform patterns in the form of bilateral spike and wave complexes) had

Table 2 continued

| Abnormalities/EEG patterns | OR  | 95 % CI    | p value | OR  | 95 % CI    | p value |
|----------------------------|-----|------------|---------|-----|------------|---------|
| FIRDA – No patients –      |     |            |         |     |            |         |
| Multiorgan failure         |     |            |         |     |            |         |
| Theta                      |     |            |         |     |            |         |
| Theta/delta                | 1.0 | 0.19–4.71  | 0.950   |     |            |         |
| Delta                      | 2.0 | 0.49–8.44  | 0.325   |     |            |         |
| Triphasic waves            | 4.0 | 1.07–14.6  | **0.039** | 6.0 | 1.24–29.4  | **0.026** |
| FIRDA                      |     |            |         |     |            |         |

FIRDA frontal intermittent rhythmic delta activity, HIV human immunodeficiency virus infection

Bold p values = significant

a Multivariable logistic regression model adjusted for all characteristics with significant values in the overall comparison (Table 1), as well as adjustment for the use of IV anesthetic drugs

Fig. 3 Differences of mean serum levels of urea and ammonia (NH3) in patients with one of the five EEG patterns. NH3 Ammonia, FIRDA frontal intermittent rhythmic delta activity
significantly higher blood urea. Demendts et al. [12] demonstrated an accurate and sensitive EEG correlation with brain dysfunction in hepatic encephalopathy, but could not show an association with ammonia levels. Remarkably, patients with TWs had high odds of death during the same hospital stay, a result that underscores the unfavorable outcome and high mortality for this encephalopathic condition [4, 34]. Our finding of increasing odds for emergence of TWs with increasing serum levels of urea and/or ammonia further emphasizes that severity may be more important than merely the presence of organ dysfunction.

Our finding of FIRDA being associated with past cerebrovascular accidents supports earlier retrospective studies that found a predominance of fixed, prior structural brain damage, such as stroke, abscesses, and encephalitis aside from non-structural metabolic encephalopathies [15]. In a prospective study, Accolla and colleagues found an independent association of structural brain lesions with the occurrence of FIRDA. They further described an association of asymmetric FIRDA with underlying focal brain lesions [1]. Early descriptions suggested a relationship between FIRDA and raised intracranial pressure [10]. Later studies, however, revealed a great variety of conditions that could be associated with FIRDA, including tumors [11, 16], subcortical lesions [24], brain edema [19], and Creutzfeld-Jacob disease [35]. As in our study, patients with FIRDA had no significant association with acute structural or non-structural abnormalities, and their outcome was mostly favorable.

The EEG patterns identified in the setting of encephalopathy were linked to clinical outcomes. Unfavorable outcome was associated with theta/delta activity and death with the presence of TWs, while favorable outcome was mainly seen in patients with FIRDA, possibly because this pattern generally reflects an old fixed structural problem (e.g., stroke). Of note, a large proportion of patients with FIRDA had a fast (theta) background activity (73%) and tended to have more intrusions of alpha activity (38%).

| Discharge destination* |
|------------------------|
| n | % | OR | 95% CI | p value** |
|-------------------------------|
| **Back home** |
| Theta | 14 | 41 | 1.7 | 0.73–3.88 | 0.226 |
| Theta/delta | 7 | 22 | 0.4 | 0.17–1.09 | 0.075 |
| Delta | 6 | 21 | 0.2 | 0.07–0.65 | 0.007 |
| Triphasic waves | 12 | 35 | 1.1 | 0.48–2.54 | 0.817 |
| FIRDA | 18 | 69 | 4.4 | 1.72–11.40 | 0.002 |

**Rehabilitation**

| n | % | OR | 95% CI | p value** |
|-------------------------------|
| Theta | 4 | 12 | 0.6 | 0.19–1.95 | 0.408 |
| Theta/delta | 4 | 13 | 0.6 | 0.20–2.02 | 0.450 |
| Delta | 13 | 46 | 9.5 | 3.40–26.3 | >0.0001 |
| Triphasic waves | 2 | 6 | 0.2 | 0.05–1.10 | 0.066 |
| FIRDA | 3 | 12 | 0.6 | 0.15–2.06 | 0.385 |

**Another hospital**

| n | % | OR | 95% CI | p value** |
|-------------------------------|
| Theta | 4 | 12 | 4.7 | 1.06–20.8 | 0.041 |
| Theta/delta | 1 | 3 | 0.6 | 0.07–4.89 | 0.608 |
| Delta | 2 | 7 | 1.3 | 0.23–7.26 | 0.775 |
| Triphasic waves | 0 | 0 | – | – | – |
| FIRDA | 1 | 4 | 0.6 | 0.07–5.04 | 0.619 |

**Skilled nursing facility**

| n | % | OR | 95% CI | p value** |
|-------------------------------|
| Theta | 9 | 97 | 0.8 | 0.34–2.03 | 0.689 |
| Theta/delta | 13 | 41 | 2.1 | 0.90–4.72 | 0.088 |
| Delta | 6 | 21 | 0.9 | 0.32–2.52 | 0.849 |
| Triphasic waves | 10 | 29 | 1.0 | 0.41–2.31 | 0.956 |
| FIRDA | 4 | 15 | 0.5 | 0.15–1.53 | 0.218 |

**Death**

| n | % | OR | 95% CI | p value** |
|-------------------------------|
| Theta | 2 | 6 | 0.2 | 0.05–1.17 | 0.077 |
| Theta/delta | 7 | 22 | 2.7 | 0.90–7.92 | 0.078 |
| Delta | 0 | 0 | – | – | – |
| Triphasic waves | 10 | 29 | 4.5 | 1.57–12.70 | 0.005 |
| FIRDA | 0 | 0 | – | – | – |

**GOS (categorical)***

| n | % | OR | 95% CI | p value** |
|-------------------------------|
| GOS >3 |
| Theta | 16 | 47 | 1.2 | 0.52–2.69 | 0.694 |
| Theta/delta | 10 | 31 | 0.4 | 0.17–0.93 | 0.033 |
| Delta | 15 | 54 | 0.9 | 0.35–2.14 | 0.748 |
| Triphasic waves | 14 | 41 | 0.8 | 0.34–1.74 | 0.530 |
| FIRDA | 21 | 81 | 4.8 | 1.63–13.90 | 0.004 |

| n | % | OR | 95% CI | p value** |
|-------------------------------|
| GOS 1–3 |
| Theta | 17 | 50 | 0.8 | 0.37–1.93 | 0.694 |
| Theta/delta | 22 | 69 | 2.5 | 1.08–5.98 | 0.033 |
| Delta | 12 | 43 | 1.2 | 0.47–2.89 | 0.748 |
| Triphasic waves | 20 | 59 | 1.3 | 0.58–2.92 | 0.530 |
| FIRDA | 5 | 19 | 0.2 | 0.07–0.61 | 0.004 |

**GOS (continuous)***

| Mean ± SD | β-coefficient | p value*** |
|-------------------------------|
| Theta | 3.5 ± 1.1 | 0.2 | 0.382 |
| Theta/delta | 3.0 ± 1.4 | −0.5 | 0.040 |
than in patients with theta background activity with (0 %) or without TWs (0 %). The trend to faster background activity in patients with FIRDA may be an additional explanation for the better outcome also reflected by their higher mean GCS. In hospitalized patients with encephalopathy, the associations of EEG abnormalities with outcomes had previously been demonstrated in patients with hepatic encephalopathy and TWs. Marchetti et al. [29] described an inverse correlation of decreasing EEG frequency in patients with cirrhosis and survival, and Bahamon-Dussan and colleagues reported poor prognosis for survival in patients with altered mental status and TWs [4]. Both studies are consistent with our findings.

One of the most important confounders in the evaluation of patients with encephalopathy can be the use of sedating intravenous drugs, since a progressive decrease in cortical activity is known to occur with increasing depth of sedation [33]. However, sedating drugs were only used in a few (13 %) patients during or 24 h prior to the EEG recording and were not used in significantly different proportions among the five EEG groups. Nevertheless, we included sedative drugs in our multivariable model. Except for the link between posterior reversible encephalopathy and delta activity, the associations identified in the univariable analyses remained significant in the multivariable models, suggesting robust associations. It is of note that the identified EEG patterns represent an intermediate state of brain dysfunction which, to a certain degree, might change significantly during the course of recovery or worsening of encephalopathy while the identified structural abnormalities in the neuroimaging represent presumably longstanding if not permanent conditions. To what degree the EEG patterns are persistent or variable over time remains unknown. The retrospective nature of this study with a consequent lack of such follow-up EEGs in most cases did not permit sufficient further analysis. Prospective studies with a repeat EEG after resolution of the acute encephalopathy would be important in this context.

There are several limitations to our study. These include the retrospective, single-center design and the size of the subgroups limiting the generalizability of our results. The patients in this study represent a highly selective sample limiting generalizability to encephalopathic patients with other or less distinct EEG patterns. It is clear that patients may have more than one of the patterns under investigation; have mixtures of transient abnormalities (e.g., FIRDA) and background abnormalities (e.g., theta); and have co-occurrences of several structural and non-structural pathologic conditions. Analyses of such specific combinations require a larger cohort. The extent to which the specific and isolated pathologic conditions had a causal role in the development of the defined EEG disturbances cannot be determined by this study. Another limitation was that the specific anatomical distribution of brain atrophy was not characterized in the analysis of neuroimaging. Finally, the procedures for obtaining noxious stimulation to produce arousal were not standardized and were arguably suboptimal.

Conclusions

In patients with encephalopathy, well-defined EEG patterns are associated with specific pathological conditions and outcome, suggesting that mechanistic hypotheses underlie these abnormal EEG patterns. To clarify the respective contributions of non-structural and structural abnormalities to encephalopathy reflected in specific EEG patterns, and to quantify the consistency of the identified patterns in association with pathologic conditions, prospective cohort studies with continuous EEG monitoring of patients with acute onset of encephalopathy are needed.

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Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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