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ORIGINAL COMMUNICATION

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 2.5, $p = 0.033$), 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

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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

background activity with or without presence of triphasic waves (TWs) and frontal intermittent rhythmic delta activity (FIRDA) [1, 7, 20]. These patterns are widely believed to reflect an underlying structural or metabolic problem; however, there is limited evidence linking specific EEG abnormalities with plausible causative factors.

The association between specific EEG patterns and circumscribed anatomical lesions has been described in both animal models and in human studies. An early model in the cat identified localized delta activity in cortex overlying circumscribed white matter lesions or localized thalamic lesions, unilateral diffuse delta activity ipsilateral to thalamic or hypothalamic lesions, and bilateral delta activity with bilateral lesions of the midbrain tegmentum [20]. Slowing of EEG background activity without slow-wave activity in the delta range has been linked to cortical impairments that spare subcortical structures. White matter abnormalities can lead to projected slow-wave activity or to TWs, while clinical entities involving both cortical and subcortical regions can induce both background slowing and slow-wave activity [25]. Despite these observations, a rigorous classification of EEG patterns and underlying causes of encephalopathy is lacking.

The aim of this study was to determine the associations between common EEG patterns and structural and non-structural abnormalities in patients with acute encephalopathy.

Materials and methods

Design and setting

This observational cohort study was performed in the Department of Neurology, Johns Hopkins Bayview Medical Center in Baltimore, USA. The study was approved by the institutional review board (ethics committee) and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Requirement for informed consent was waived.

Patient selection and data collection

We identified hospitalized patients from October 2007 to February 2012 who underwent EEG to evaluate an acute alteration in mental status. Based on the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association, acute alteration in mental status was defined as altered consciousness and/or change in cognition (i.e., memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that was not better accounted for by a preexisting, established or evolving dementia. The disturbance had to have developed over a short time period (hours to days) [2]. EEGs were classified by two certified electroencephalographers 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 consisting 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 appearance 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 discharges, 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 of EEG, critical illnesses, and critical interventions including hemodialysis, mechanical ventilation and cardiopulmonary 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 glucose, 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 previously 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

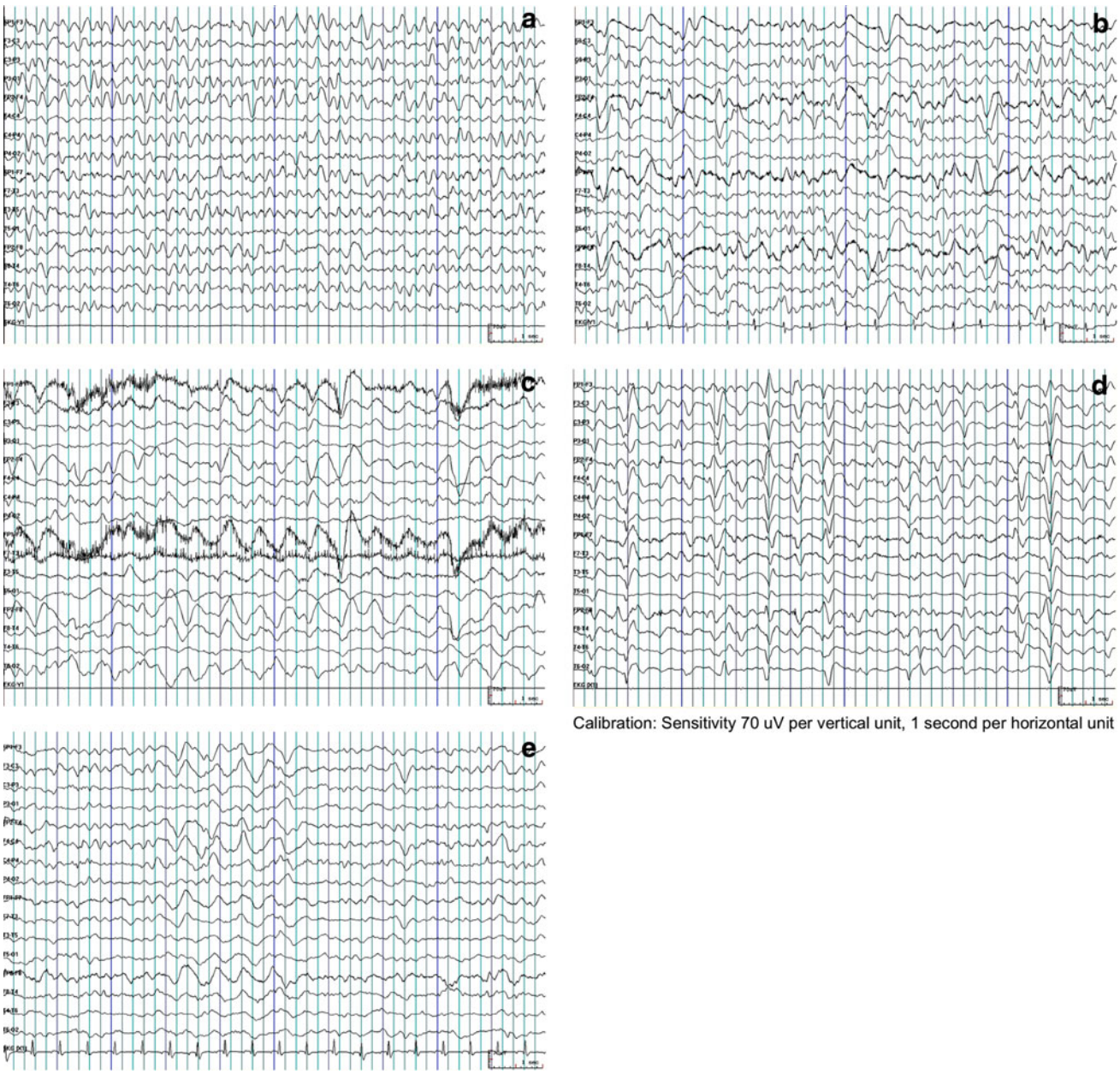

Fig. 1 Examples of the five different EEG patterns in encephalopathic patients: **a** generalized slow background activity of 4–7 Hz (theta); **b** generalized slow background activity of 4–7 Hz with intrusions of delta activity (theta/delta); **c** generalized delta background activity (delta); **d** 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)

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

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 colinearity, 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 ($\pm$18) years with 43 % males and 57 % females. The mean of the lowest GCS on the day of EEG recording was 11 ($\pm$4). The majority of patients (70 %) were in the ICU including neurocritical care unit (38 %), medical intensive care unit (21 %), cardiac (10 %), and surgical care unit (2 %). All other patients were hospitalized on the neurological or medical wards. Only 13 % of patients received intravenous sedative or anesthetic drugs during or 24 h before EEG (11 had lorazepam, 6 midazolam, and 3 propofol) without significant differences between the five patients groups ($p = 0.378$). The most prevalent critical illness was renal insufficiency in 55 %, followed by respiratory failure (10 %), liver insufficiency (8 %), septic shock (6 %), and acute lung injury or acute respiratory distress syndrome (2 %). Cerebral CT was performed in 38 and 62 % of patients who received brain MRI. Mean time between EEG and neuroimaging was 2 ($\pm$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-occuring 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, $p = 0021$, 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 (κ 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

Table 1 Demographics and clinical features of patients with different EEG patterns in encephalopathy ($n = 154$)

Demoghraphics	Theta ($n = 34$)		Theta/delta ($n = 32$)		Delta ($n = 28$)		Triphasic waves ($n = 34$)		FIRDA ($n = 26$)		p value*
	n	%	n	%	n	%	n	%	n	%	
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	7	21	2	8	0.127
Bacteremia	7	21	2	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**
Autoimmundisease	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

Table 1 continued

Demoghraphics	Theta ($n = 34$)		Theta/delta ($n = 32$)		Delta ($n = 28$)		Triphasic waves ($n = 34$)		FIRDA ($n = 26$)		p value*
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	
Moderate	8	24	11	34	9	32	9	27	6	23	0.818
Marked	7	21	7	22	8	29	6	18	3	12	0.633
Atrophy	22	65	13	41	10	36	15	44	9	35	0.108
Mild	9	27	6	19	6	21	7	21	7	27	0.533
Moderate	11	32	5	16	3	11	11	32	2	8	**0.036**
Marked	2	6	2	6	1	4	0	0	0	0	0.501

CNS central nervous system, *ARDS* acute respiratory distress syndrome, *ALI* acute lung injury, *HIV* human immunodeficiency virus

Bold p values = significant

* Analysis of variance (ANOVA) for continuous variables; Pearson's Chi-square test with Fisher's exact test were appropriate for categorical variables

[a] Values are expressed as mean ± SD

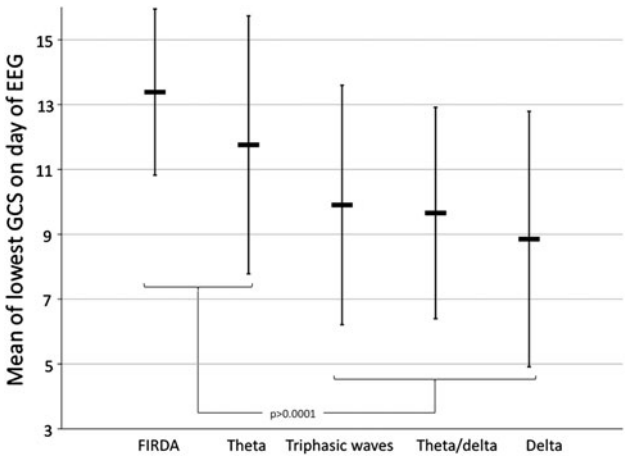

Fig. 2 Mean of lowest GCS on day of EEG in patient groups with one particular EEG pattern. *GCS* Glasgow Coma Scale, *FIRDA* frontal intermittent rhythmic delta activity. Adjusted for the use of intravenous (IV) anesthetic drugs

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-occuring 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

Table 2 Associations between structural and non-structural abnormalities and particular EEG patterns in encephalopathic patients ($n = 154$)

Crude				Adjusted[a]		
Abnormalities/EEG patterns	OR	95 % CI	*p* value	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	–	No patients	–			
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	–	No patients	–			
Theta/delta	–	No patients	–			
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	–	No patients	–			
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	–	No patients	–			
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**

Table 2 continued

Crude				Adjusted[a]		
Abnormalities/EEG patterns	OR	95 % CI	*p* value	OR	95 % CI	*p* value
FIRDA	–	No patients	–			
Multiorgan failure						
Theta	–	No patients	–			
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	–	No patients	–			

FIRDA frontal intermittend 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

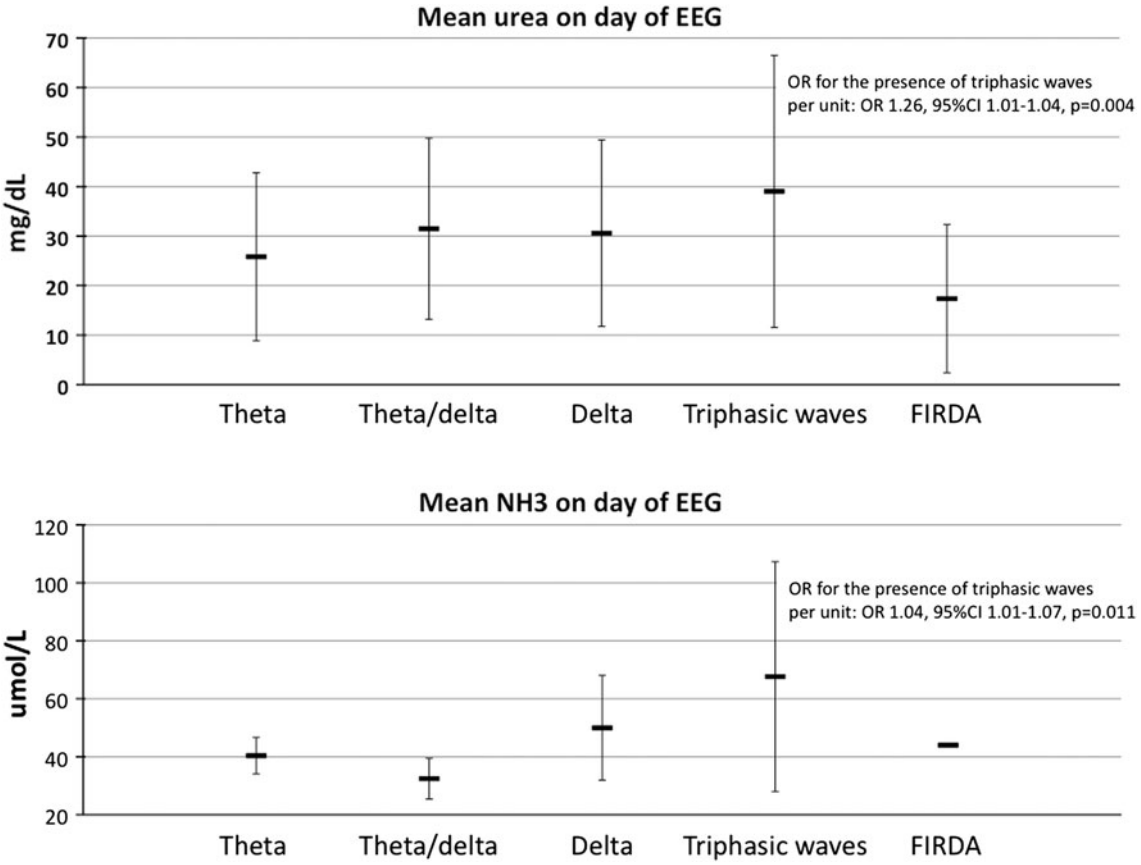

Fig. 3 Differences of mean serum levels of urea and ammonia (NH3) in patients with one of the five EEG patterns. NH_3 Ammonia, *FIRDA* frontal intermitted rhythmic delta activity

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 3 Categorical and continuous short-term outcomes ($n = 154$)

	n	%	OR	95 % CI	*p* value**
Discharge destination*					
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					
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					
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					
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					
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)*					
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**
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**
Delta	3.7 ± 0.9	−0.02	0.955
Triphasic waves	2.9 ± 1.4	−0.5	**0.018**
FIRDA	4.4 ± 0.8	1.0	**<0.0001**

FIRDA frontal intermittent rhythmic delta activity, *GOS* Glasgow Outcome Scale

Bold *p* values = significant

* Data regarding outcome were missing for two patients (one for the theta, one for the delta group)

** Multivariable logistic regression model adjusted for age

*** Multivariable linear regression model adjusted for age

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 %)

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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