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ORIGINAL WORK

Neurological Prognostication After Hypoglycemic Coma: Role of Clinical and EEG Findings

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Abstract

Background: Hypoglycemic coma (HC) is an uncommon but severe clinical condition associated with poor neurological outcome. There is a dearth of robust neurological prognostic factors after HC. On the other hand, there is an increasing body of literature on reliable prognostic markers in the postanoxic coma, a similar—albeit not identical—situation. The objective of this study was thus to investigate the use and predictive value of these markers in HC.

Methods: We conducted a retrospective, multicenter, cohort study within five centers of the Critical Care EEG Monitoring Research Consortium. We queried our electroencephalography (EEG) databases to identify all patients undergoing continuous EEG monitoring after admission to an intensive care unit with HC (defined as Glasgow Coma Scale < 8 on admission and a first blood glucose level < 50 mg/dL or not documented but in an obvious clinical context) between 01/01/2010 and 12/31/2020. We studied the association of findings at neurological examination (Glasgow Coma Scale motor subscale, pupillary light and corneal reflexes) and at continuous EEG monitoring(highly malignant patterns, reactivity, periodic discharges, seizures) with best neurological outcome within 3 months after hospital discharge, defined by the Cerebral Performance Category as favorable (1–3: recovery of consciousness) versus unfavorable (4–5: lack of recovery of consciousness).

Results: We identified 60 patients (30 [50%] women; age 62 [51–72] years). Thirty-one and 29 patients had a favorable and unfavorable outcome, respectively. The presence of pupillary reflexes (24 [100%] vs. 17 [81%]; *p* value 0.04) and a motor subscore > 2 (22 [92%] vs. 12 [63%]; *p* value 0.03) at 48–72 h were associated with a favorable outcome. A highly malignant EEG pattern was observed in 7 of 29 (24%) patients with unfavorable outcome versus 0 of 31 (0%) with favorable outcome, whereas the presence of EEG reactivity was observed in 28 of 31 (90%) patients with favorable outcome versus 13 of 29 (45%) with unfavorable outcome ($p < 0.001$ for comparison of all background categories).

Conclusions: This preliminary study suggests that highly malignant EEG patterns might be reliable prognostic markers of unfavorable outcome after HC. Other EEG findings, including lack of EEG reactivity and seizures and clinical findings appear less accurate. These findings should be replicated in a larger multicenter prospective study.

Keywords: Patient outcome assessment, Diabetic coma, Electroencephalography, Neurologic examination

Introduction

Hypoglycemia is a frequent complication in a patient with diabetes mellitus and can also occur in other conditions. A broad range of neurological complications are associated with hypoglycemia, including coma [1–3]. Hypoglycemic coma (HC) is defined as prolonged coma

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secondary to hypoglycemia (blood glucose level < 50 mg/dL) and exclusion of other causes [4–6]. Insulin or oral hypoglycemic agent overdose, malnutrition, alcohol abuse, insulin-secreting tumors, and liver failure are the main causes [7, 8]. Neurological outcome after HC ranges from the full recovery of consciousness and autonomy to irreversible brain damage with persistent vegetative state or brain death [9]. Known clinical risk factors of unfavorable outcome include the depth and duration of hypoglycemia, initial body temperature and blood lactate levels [4–6]. There is currently a dearth of robust prognostic biomarkers after HC. Brain magnetic resonance imaging (MRI) may provide useful prognostic information but is not often performed [10–14]. There is a need for additional clinical indicators of outcome to improve the accuracy of prognostication and avoid premature withdrawal of life support therapies (WLST) and futile treatments. Improvement in prognostication may also facilitate the allocation of resources to those patients with the potential for recovery.

In HC and postanoxic coma, the brain is temporarily deprived of at least one of its main metabolic substrates. Prognostication following anoxic brain injury now follows a multimodal approach, which includes neurological examination, continuous electroencephalographic monitoring (CEEG), somatosensory evoked potentials (SSEPs), neuron-specific enolase (NSE) levels, and brain imaging [10]. This multimodal approach, especially EEG [15, 16], has been shown to provide accurate predictions for a favorable outcome and an unfavorable outcome.

We thus hypothesized that known predictors of outcome in postanoxic coma would also provide prognostic information in HC. The objectives of this study were to investigate the predictive value of multimodal biomarkers in HC, with a primary focus on the predictive value of CEEG. Our secondary aim was to determine the predictive value of neurological examination, SSEPs, NSE levels, and brain MRI in HC. We also aimed to assess how often these modalities were used either individually or in combination in clinical practice.

Methods

Study Design and Ethical Approval

This was a retrospective multicenter cohort study within five centers of the Critical Care EEG Monitoring Research Consortium: Yale University (New Haven, CT); Brigham and Women' Hospital (Boston, MA); University of Pittsburgh Medical Center (Pittsburgh, PA); University of Wisconsin, Madison (Madison, WI); and Hôpital Erasme (Brussels, Belgium). All procedures were approved by the ethics committee/institutional review board of each institution, and a waiver of consent was granted.

Inclusion and Exclusion Criteria

We queried our EEG databases to identify all patients who underwent CEEG after admission to an intensive care unit (ICU) with HC (defined as GCS < 8 on admission and glucose < 50 mg/dL or GCS < 8 on admission and undocumented first blood glucose level but in an obvious context [i.e., otherwise unexplained in a patient with diabetes]) between 01/01/2010 and 12/31/2020. Patients with coma explained by an associated concomitant cause were excluded.

Clinical Variables

Clinical variables were retrieved from our prospective CEEG database or by retrospective chart review. We recorded age, sex, cause of HC (categorized as insulin overdose, other medication overdose, gastrointestinal or liver disease and other), functional status prior to admission with Cerebral Performance Category (CPC) score [17], and history of chronic alcohol abuse, drug abuse, or diabetes mellitus. We also recorded the GCS [18] on admission, the occurrence of convulsions prior to CEEG, pretreatment blood glucose level, estimated duration of hypoglycemia (categorized as < 1 h, 1–5 h, > 5 h), body temperature, lactate level, and pH on admission, ICU complications (including sepsis, pneumonia), ICU length of stay, WLST, myoclonus during ICU stay, corneal reflexes, pupillary light reflexes and motor response at 48–72 h, brain CT findings (including brain edema), brain MRI findings (including cortical restricted diffusion, deep gray matter restricted diffusion, no restricted diffusion), presence or absence of SSEPs N20, and highest NSE levels (mg/dL).

We retrieved CEEG findings from reports, including background findings (continuity, reactivity), and the presence of periodic discharges (PDs), electrographic seizures (ESz) according to a standardized terminology [19]. Electrographic status epilepticus (ESE) was defined as ESz lasting more than 10 min. In case reactivity assessment was performed multiple times during CEEG, it was deemed present if it was observed at least once. Similarly, the occurrence of a PDs or ESz/ESE at any moment during monitoring, even transiently, was sufficient to qualify as present. If multiple background patterns were present at different times of the recording, the worst pattern was used. We further classified the EEG findings using categories derived from the postanoxic literature [20–24] as highly malignant patterns (suppression-burst, PDs on a suppressed background, persistent suppression) versus nonhighly malignant and as reactive versus nonreactive. This classification was performed by one of the authors (NG), anonymized to other data.

Best outcome within 3 months after discharge was assessed with the CPC score [20] on the basis of information available in medical charts. This included discharge outcome data and follow-up data, when available. A favorable outcome was defined as CPC ≤ 3 (indicating recovery of consciousness).

Statistical analysis

Variables were summarized using descriptive statistics (median [interquartile range] or count [percentage]) and compared between cases with favorable (CPC ≤ 3) and unfavorable outcome (CPC 4–5) using nonparametrical tests (Mann–Whitney *U* test) for ordinal variables and Chi^2 or Fisher exact test for categorical variables. The prognostic accuracy of variables significantly associated with outcome was reported as sensitivity and false positive rate (FPR). To assess the presence of a potential bias of therapeutic limitations on the prognostic values of investigated variables, we also carried a subgroup analysis in patients in whom withdrawal or withholding of life support therapies did not occur. Statistical significance was predetermined as a two-tailed p value < 0.05. Statistics and data visualization were computed on the open-source JASP, Version 0.14.1 (https://www.jasp-stats.org).

Results

Study Cohort and Outcome

We identified a total of 60 patients (30 [50%] women; age: 62 [51–72] years) in the five centers fulfilling our inclusion criteria (Table 1). The main causes were insulin (58%) or another hypoglycemic agent overdose (8%). Forty-four (73%) patients had diabetes, 30 (50%) were chronic alcohol abusers, and 17 (28%) had substance use disorder. The majority (55 [92%]) of patients had a good functional status prior to admission. Their ICU length of stay was 8 (4–13) days, and the main complications during the ICU stay were pneumonia (21 [35%]) and sepsis (10 [17%]). Life support therapies were withdrawn for 26 patients (43%). Twenty (33%) patients died during their hospital stay, 9 (15%) were unconscious, and 31 (53%) were conscious at time of hospital discharge. Follow-up data were available in 35 patients. This included data for 8/9 unconscious patients who all died after discharge without regaining consciousness. Thus, 31 (53%) patients ultimately recovered consciousness. Conversely, 29 had an unfavorable outcome. Of all the clinical variables, only WLST was associated with outcome (2 [6%] vs. 2 4[43%], respectively, in the favorable versus unfavorable outcome groups; $p < 0.001$).)

HC Features

The median GCS on admission was 5 (4–7) (Table 1). Initial blood glucose level ($n = 41$) was 25 (20–35) mg/dL. The estimated duration of hypoglycemia ($n = 34$) was > 5 h in 11 (33%), 1–5 h in 14 (42%) and < 1 h in 9 (27%). Body temperature ($n = 58$) was 36.7 °C (35.3–37.6), arterial lactate levels ($n = 56$), and arterial blood pH on admission ($n = 54$) were 2.1 (1.2–3.7) mg/dL and 7.39 (7.31–7.45), respectively. 21 of 60 patients had convulsions prior to admission (35%).

Neurological Examination

Myoclonus occurred during the ICU stay in 23 (38%) patients (Table 1). At 48–72 h after admission, corneal and pupillary light reflexes were present in 32/36 (89%) and 41/45 (91%) patients, respectively, and a GCS motor subscale > 2 was present in 34/43 (79%).

Both the presence of pupillary reflexes (24 [100%] vs. 17 [81%]; p value 0.04) and a motor subscale > 2 (22 [92%]; 12 [63%]; p value 0.03) at 48–72 h were associated with favorable neurological outcome.

Continuous EEG Findings

Continuous EEG was started a median of 2 (1–4) days after admission. Findings are summarized in Table 2.

Of the 60 patients, 27 (44%) had PDs and their presence was associated with an unfavorable outcome (10 [32%] vs. 17 [59%]; $p = 0.04$). The prevalence of PDs was rare or occasional in 6 (22%) frequent in 4 (15%), and abundant or continuous in 17 (63%). Twelve (20%) had ESz or ESE, including four with myoclonic SE/Sz and eight nonconvulsive SE/Sz and their presence tended to be associated with unfavorable outcome (3 [10%] vs. 9 [31%]; $p = 0.054$).

Background was classified as highly malignant in 7 (12%) cases, all with unfavorable outcome, and nonhighly malignant in 53, of which 31 (60%) had a favorable outcome ($p = 0.004$). Among patients with highly malignant patterns, CEEG was started within the first 24 h of admission in two, and more than 24 h after admission in five. Highly malignant patterns were still present after 24 h of admission in all cases. Reactivity was present in 41 (68%), of which 28 had a favorable outcome, and absent in 19 (32%), of which 13 had a poor outcome ($p < 0.001$). No patient with a highly malignant background showed reactivity.

Additional Clinical Findings

Brain CT scans were performed in 54 (90%) patients (Table 2); 3/54 (6%) showed global brain edema. Brain MRI was performed in 39 (65%). Restricted diffusion in gray matter was observed in 18 [46%], including in the cortex (12 [31%]) and in the deep gray structures (11/39 [28%]), and was associated with unfavorable outcome (12/15 [80%] vs. 6/24 [25%]; $p = 0.001$).

Table 1 Demographic and clinical features

Parameter	Total ($N=60$)	Did not regain consciousness (CPC 4–5; $n=29$)	Did regain consciousness (CPC 1–3; $n=31$)	*p* value
Age (y)	62 (51–72)	63 (52–74)	59 (46–68)	0.26
Female sex	30 (50)	13 (45)	17 (55)	0.44
Cause				
Insulin	35 (58)	17 (59)	18 (58)	0.79
Other medication	5 (8)	2 (7)	3 (10)	
GI or Liver	6 (10)	2 (7)	4 (13)	
Other	14 (23)	8 (28)	6 (19)	
Good functional status prior to admission (CPC 1–2)	55 (92)	27 (93)	28 (90)	1
History of diabetes mellitus	44 (73)	19 (66)	25 (81)	0.3
History of chronic alcohol abuse	30 (50)	14 (48)	16 (52)	1
History of drug abuse	17 (28)	9 (31)	8 (26)	0.78
GCS on admission	5 (4–7)	4 (3–6)	6 (5–7)	**0.01**
Convulsions prior to CEEG	21 (35)	9 (31)	12 (39)	0.73
Initial blood glucose level (mg/dL; $n=41$)	25 (20–35)	27 (20–32)	23 (20–35)	0.36
Estimated duration of hypoglycemia (min; $n=34$)				
> 5 h	11 (33)	9/23 (39)	2/11 (18)	0.38
1 to 5 h	14 (42)	9/23 (39)	5/11 (45)	
< 1 h	9 (27)	5/23 (22)	4/11 (36)	
Body temperature on admission (°C; $n=58$)	36.7 (35.3–37.6)	37.0 (36.4–37.7)	35.8 (35.1–37.6)	0.79
Lactate level on admission (mg/dl; $n=56$)	2.1 (1.2–2.7)	1.9 (1.2–3.1)	2.3 (1.4–4.4)	0.23
pH on admission ($n=54$)	7.39 (7.31–7.45)	7.40 (7.34–7.43)	7.36 (7.31–7.38)	0.48
ICU complications				
Pneumonia	21 (35)	8 (28)	13 (42)	0.27
Sepsis	10 (17)	5 (17)	5 (16)	1
ICU length of stay (d)	8 (4–13)	8 (4–15)	8 (5–12)	0.78
Withdrawal/withholding of life support therapy	26 (43)	24 (83)	2 (6)	**< 0.001**
Myoclonus during ICU stay ($n=60$)	23 (38)	14/29 (48)	9/31 (29)	0.18
Corneal reflexes at 48–72 h ($n=36$)	32 (89)	17/20 (85)	15/16 (94)	0.61
Pupil reflexes at 48–72 h ($n=45$)	41 (91)	17/21 (81)	24/24 (100)	**0.04**
GCS-M > 2 at 48–72 h ($n=43$)	34 (79)	12/19 (63)	22/24 (92)	**0.03**

Data are presented as count (percentage) or median (interquartile range)

Bold values indicate statistical significance

CEEG, continuous electroencephalograpm, CPC, Cerebral Performance Categories, GCS, Glasgow Coma Scale, GCS-M, Glasgow Coma Scale motor subscale, GI, gastrointestinal, GPDs, generalized periodic discharges, ICU, intensive care unit, MRI, magnetic resonance imaging, NSE, neuron specific enolase, SSEPs, somatosensory evoked potentials

SSEPs were performed in only eight (100%) patients and showed present N20 in all cases, including six with unfavorable outcome. NSE levels were available in only four cases, and were elevated in one case, which did have an unfavorable outcome.

The sensitivity and FPR of variables significantly associated with absence of return to consciousness are presented in Table 3. The presence of restricted diffusion in cortical regions or deep gray matter had the highest sensitivity (80%) but with a high FPR (25%), whereas the lack of EEG reactivity and the presence of a highly malignant EEG background had the lowest FPR (10% and 0%, respectively) but with a lower sensitivity (40% and 24%, respectively).

Effect of Therapeutic Limitations on Prognostic Values

In the subgroup of patients for whom WLST did not occur ($n=34$), only EEG variables remained significantly associated with outcome. A highly malignant background was observed in three cases, all with unfavorable outcome, and nonhighly malignant background in 31,

Table 2 Results from continuous EEG and other tests

Parameter	Total ($N=60$)	Did not regain consciousness (CPC 4–5; $n=29$)	Did regain consciousness (CPC 1–3; $n=31$)	*p* value
CEEG findings				
Periodic discharges	27 (44)	17 (59)	10 (32)	**0.04**
GPDs	21 (35)	11 (38)	10 (32)	
BIPDs	3 (5)	3 (10)	0 (0)	
LPDs	3 (5)	3 (10)	0 (0)	
ESE/Esz	12 (20)	9 (31)	3 (10)	**0.05**
Myoclonic ESE/ESz	4 (7)	3 (10)	1 (3)	
NCSE/NCSz	8 (13)	6 (21)	2 (6)	
Background				
Reactive versus nonreactive	41 (68)	13 (45)	28 (90)	**< 0.001**
Highly malignant versus nonhighly malignant	7 (12)	7 (24)	0 (0)	**0.004**
Suppression-burst	3 (5)	3 (10)	0 (0)	
Suppression-PDs	3 (5)	3 (10)	0 (0)	
Persistent suppression	1 (2)	1 (3)	0 (0)	
Time from admission to CEEG (d)	2 (1–4)	1 (1–4)	2 (1–4)	0.51
CT findings ($n=54$)				
Brain edema	3/54 (6)	2/25 (8)	1/29 (3)	0.6
Time from admission to CT (d)	0 (0–0)	0 (0–1)	0 (0–0)	0.84
MRI findings ($n=39$)				
Restricted diffusion, cortical	12/39 (31)	8/15 (53)	4/24 (17)	**0.03**
Restricted diffusion, deep gray matter	11/39 (28)	7/15 (47)	4/24 (17)	0.07
Restricted diffusion, any	18/39 (46)	12/15 (80)	6/24 (25)	**0.001**
Time from admission to MRI (d)	3 (2–6)	4 (2–8)	2 (1–6)	0.16
SSEPs N20 present (n = 8)	8/8 (100)	6/6 (100)	2/2 (100)	1
Time from admission to SSEPs (d)	4 (3–7)	6 (3–8)	3 (3–3)	Na
Highest NSE levels > 33 mg/dL, ($n=4$)	1/4 (25)	1/4 (25)	Na	Na

Data are presented as count (percentage) or median (interquartile range)

Bold values indicate statistical significance

BIPDs, bilateral independent periodic discharges, CEEG, continuous electroencephalogram, CPC, Cerebral Performance Categories, CT, computed tomography, ESE, electrographic status epilepticus, ESz, electrographic seizures, GPDs, generalized periodic discharges, LPDs, lateralized periodic discharges, MRI, magnetic resonance imaging, Na, not available, NSE, neuron specific enolase, PDs, periodic discharges, SSEPs, somatosensory evoked potentials

of which 29 (94%) had a favorable outcome ($p=0.002$). Reactivity was present in 27 patients, of whom 25 had a favorable outcome, and absent in 7, of whom 2 had a poor outcome ($p=0.048$).

Discussion

In this retrospective multicenter cohort study, we identified prognostic features in 60 patients admitted to an ICU with HC and who underwent CEEG.

The main finding is the significant prognostic value of the CEEG background, in particular the highly malignant patterns that were exclusively present in patients with an unfavorable neurological outcome. To a lesser degree, lack of EEG reactivity was also associated with an unfavorable outcome. To our knowledge, this is the first time that such observations are made in HC. Only one study previously investigated the prognostic value of EEG in patients with HC [5]. In that particular study, EEG findings were categorized as normal (in only one patient) or abnormal and were not associated with patients' outcome. Our results are in line with the now extensive literature on the prognostic value of highly malignant patterns and EEG reactivity in postanoxic coma [10, 20–24]. PDs and SE or Sz, including myoclonic SE and Sz, were also associated with unfavorable outcome, but not exclusively. Hence, again similarly to postanoxic coma, their presence should not be regarded as an infallible prognostic sign [20, 24]. Continuous EEG was usually not started within the first 24 h of admission, which might have led to an underestimation of its prognostic value. Indeed, in postanoxic coma, CEEG findings during the first 24 h are the most significant [25]. Continuous sedation with propofol,

Table 3 Sensitivity and false positive rate of predictors associated with lack of recovery of consciousness

Parameter	Sensitivity (%)	False positive rate (%)
Clinical findings		
Lack of pupil reflexes at 48–72 h	19	0
GCS-M ≤ 2 at 48–72 h	37	8
CEEG findings		
Periodic discharges	59	32
ESE/Esz	31	10
Lack of reactivity	45	10
Highly malignant background	24	0
MRI findings ($n = 39$)		
Restricted diffusion, cortical or deep gray matter	80	25

CEEG, continuous electroencephalogram, ESE, electrographic status epilepticus, ESz, electrographic seizures, GCS-M, Glasgow Coma Scale motor subscale, MRI, magnetic resonance imaging

and to a lesser extent with midazolam, can alter reactivity and cause suppression-burst, a highly malignant pattern, and thus might confound the predictive value of EEG in HC. Further studies should thus investigate this potential confounding effect.

We also found an association between abnormal findings on neurological examination and outcome, especially the motor assessment and pupillary reflexes. To the best of our knowledge, there are no data on the prognostic value of the neurological examination in HC. Our findings are however in line with the available evidence in postanoxic comatose patients, in which a poor motor response and the bilateral absence of pupillary light reflex at 72 h after arrest are considered strong, albeit not perfectly accurate, predictors of unfavorable prognosis (FPR 0–4%) [25]. Several studies showed that the distribution of neuronal necrosis and the biochemical mechanisms underlying the two entities are different [12]. Indeed, the thalamus is a structure that is largely spared in HC, whereas it is frequently subject to lesions in postanoxic coma. It seems that this is also the case in the brain stem where protein synthesis remains relatively unaffected in HC compared with postanoxic coma [12]. Therefore, we know that some brain structures are more sensitive to anoxia than to hypoglycemia and vice versa. Along these lines, the brainstem may be more resistant to hypoglycemia than to anoxia, which could explain why the absence of brainstem reflexes is less frequent in our sample than in postanoxic coma.

We found that brain imaging is almost always done in clinical practice, and that brain MRI is more sensitive than brain CT, as previously reported [5]. The presence of cortical or deep gray nuclei DWI abnormalities was associated with unfavorable outcome, as previously reported [12]. However, as many as 25% of patients with a favorable outcome showed restricted diffusion in the cortex or deep gray matter, which contradicts results from several studies that reported a much higher specificity [11, 12, 26–28]. This discrepancy might result from several reasons. We relied on clinical reports and did not standardize imaging assessment. Also, not only the presence, but also the location, extent and reversibility of DWI abnormalities are associated with outcome [11, 12, 26–28]. Finally, we did not quantify diffusion abnormalities, using apparent diffusion coefficient for instance, an approach that was recently show to have excellent accuracy, possibly superior to visual analysis [28].

Our study has several limitations. It was a retrospective study, and some variables were not always available in the patients' records, such as the duration of hypoglycemia and initial blood glucose level, a limitation that is shared with almost all studies on the subject. As in all studies on prognosis, worrisome EEG findings might have led to therapeutic limitations and "self-fulfilling prophecies," although none of the centers did explicitly use a standardized prognostication strategy. In addition, EEG findings remained associated with outcome in the subgroup of patients in which such limitations did not occur, possibly because EEG were not requested for prognostication purposes. Conversely, clinical EEG readers were not masked to clinical data during the acute, which might have affected the interpretation of EEG findings. Some ancillary tests (SSEPs, NSE) were only performed in a handful of patients, and we could not draw any conclusion on their clinical use. We included only patients who received CEEG, which might have led to an inclusion bias. It is for instance possible that only patients with persistent coma were included, although most CEEG were performed within 4 days of admission. More likely, our sample might have been biased toward those patients with clinical seizures, as it is the most frequent indication for CEEG, which might explain the high rate of ESE/ESz and PDs that we observed. Our findings might not be generalizable to all patients with HC. Yet, our series is multicentric and currently one of the largest available series. EEG patterns evolve with time after anoxic brain injury and patterns with the most significant predictive value are mostly present during the first 24 h after the injury [23, 24]. CEEG was started after a median of 2 days in this cohort, and we only reported a single description of EEG findings rather than providing information on temporal evolution, and thus potentially leading to underestimating its predictive value. We focused our study on predictors that are currently considered strong predictors of outcome in postanoxic coma. Emerging modalities, such as automated pupillometry, should be studied as well. Finally, although this is the largest sample of patients with HC receiving CEEG to date, our sample size remains modest and our findings need to be replicated in a larger prospective study.

Conclusions

Our findings suggest a potential role for CEEG to complement the neurological examination in the prognostication of HC. Similar to postanoxic coma, highly malignant patterns are associated with unfavorable neurological outcome, whereas the presence of reactivity is associated with favorable neurological outcome. These findings need to be replicated in future prospective studies. Because of the very limited data available, we could not draw any conclusion on the role of NSE and SSEPs in this setting. Similarly, the lack of quantitative analysis precludes any conclusion on the use of brain MRI. These modalities also deserve further investigations.

Supplementary Information

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Author Contributions

DB: study conception and design, acquisition, analysis, and interpretation of data; drafting the article and revising it critically for important intellectual content. TP: acquisition, analysis, and interpretation of data; drafting the article and revising it critically for important intellectual content. NR: acquisition, analysis, and interpretation of data; drafting the article and revising it critically for important intellectual content. SF: acquisition, analysis, and interpretation of data; drafting the article and revising it critically for important intellectual content. JFI: study conception and design, acquisition of data, analysis, and interpretation of data; drafting the article and revising it critically for important intellectual content. EJG: study conception and design, acquisition of data, analysis, and interpretation of data; drafting the article and revising it critically for important intellectual content. JWL: study conception and design, acquisition of data, analysis, and interpretation of data; drafting the article and revising it critically for important intellectual content. AFS: study conception and design, acquisition of data, analysis, and interpretation of data; drafting the article and revising it critically for important intellectual content. NG: study conception and design, acquisition of data, analysis, and interpretation of data; drafting the article and revising it critically for important intellectual content. The final manuscript was approved by all authors.

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None.

Declarations

Ethical Approval/Informed Consent

We adhered to ethical guidelines and indicate ethical approvals (institutional review board) and the use of informed consent, as appropriate.

Conflicts of interest

EJG receives National Institutes of Health funding from National Institute of Neurological Disorders and Stroke, is a consultant for Union Chimique Belge and a co-founder of Intracranial Bioanalytics. JWL: contract work (Bioserenity, Teladoc); consultant (Biogen); co-founder (Soterya Inc); and research funding (Epilepsy Foundation; site PI, NIH UH3HL145269; R01NS062092). The remaining authors have no conflicts to disclose.

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