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Original Investigation

Associated Factors and Prognostic Implications of Stimulus-Induced Rhythmic, Periodic, or Ictal Discharges

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IMPORTANCE The implications of stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs) sometimes found on prolonged electroencephalographic (EEG) recordings are uncertain.

OBJECTIVE To evaluate the incidence of SIRPIDs and their clinical implications in critically ill patients.

DESIGN, SETTING, AND PARTICIPANTS A multicenter, international retrospective study was performed from October 1, 2012, through September 30, 2014, of consecutive adult patients hospitalized in intensive care units with alteration of consciousness who underwent EEG recordings at 3 separate centers. Demographic data, including admission diagnosis, age, sex, history of epilepsy, and EEG findings, were noted. Characteristics of SIRPIDs were documented. Data were evaluated for predictors of SIRPIDs and in-hospital mortality. Data analysis was performed from January 16, 2015, to June 15, 2015.

MAIN OUTCOMES AND MEASURES Incidence of SIRPIDs, association of SIRPIDs with mortality and other EEG characteristics, and EEG and clinical predictors of mortality.

RESULTS A total of 416 patients were studied. The median age of patients was 60 years (interquartile range, 46-71 years), and 252 (60.6%) were male. A total of 104 patients (25.0%) did not survive to hospital discharge. SIRPIDs were identified in 43 patients (10.3%). The proportion of patients with SIRPIDs was not significantly different across the 3 sites ($P = .34$). Anoxic brain injury (odds ratio [OR], 3.80; 95% CI, 1.73-8.33; $P < .001$), the use of antiepileptic medications (OR, 3.24; 95% CI, 1.31-8.00; $P = .01$), electrographic seizures (OR, 2.85; 95% CI, 1.13-7.19; $P = .03$), generalized periodic discharges with triphasic morphologic features (OR, 3.66; 95% CI, 1.67-8.02; $P = .001$), and sporadic sharp waves and periodic discharges (OR, 2.59; 95% CI, 1.13-5.92; $P = .02$) were independently associated with the presence of SIRPIDs. Older age (OR, 1.02; 95% CI, 1.01-1.04; $P = .005$), anoxic brain injury (OR, 3.49; 95% CI, 1.96-6.21; $P \leq .001$), and absence of EEG reactivity (OR, 8.14; 95% CI, 4.20-15.79; $P < .001$) but not SIRPIDs (OR, 1.73; 95% CI, 0.79-3.78; $P = .17$) were independently associated with in-hospital mortality.

CONCLUSIONS AND RELEVANCE In critically ill patients undergoing EEG recordings, SIRPIDs occurred in 43 (10.3%) and were associated with other electrographic abnormalities previously reported to indicate poor prognosis. However, SIRPIDs were not independently associated with in-hospital mortality.

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Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs) are an electroencephalographic (EEG) finding seen in the critical care setting that were first described in 2004 (**Figure**).[1] SIRPIDs may be present in 12% to 22% of patients undergoing EEG recordings in the intensive care unit (ICU).[1-3] Identified causes of SIRPIDs include primary cerebral symptoms, such as intracranial hemorrhages,[1] neurodegenerative diseases,[4] and traumatic brain injury,[3] and systemic symptoms, such as anoxic brain injury,[1-3,5] metabolic disturbances,[1] and drug toxicity.[6] The pathophysiologic mechanisms and ultimate clinical implications of SIRPIDs remain uncertain. Some data suggest that they do not represent an ictal pattern as evidenced by negative single-photon emission computed tomography results[7,8]; however, clinical improvement and resolution of SIRPIDs have been reported after treatment with benzodiazepines.[9]

Despite an increasing body of data regarding SIRPIDs, their prognostic value remains unknown, and large studies evaluating this question are lacking. One study[10] that investigated comatose patients with periodic discharges (PDs), including SIRPIDs, did not find a difference in outcome or survival compared with a group of patients without PDs. A study[2] specifically looking at the prognostic utility of SIRPIDs in comatose patients after cardiac arrest found that they were associated with mortality when present during the hypothermic period but not when exclusively seen in the posthypothermia period. Another study[3] found no difference in outcomes between patients with and without SIRPIDs. Thus, data on the prognostic significance of SIRPIDs are limited and conflicting. The aim of this study was to evaluate the prognostic value of SIRPIDs in critically ill patients with altered mental status in the ICU at 3 separate centers.

Key Points

Question: Do stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs) have a prognostic value in critically ill patients with encephalopathy?

Findings: In our population of intensive care unit patients undergoing electroencephalography, 43 (10.3%) had evidence of SIRPIDs. Other electroencephalographic abnormalities were also common in this population.

Meaning: SIRPIDs do not appear to independently predict mortality, but they often accompany other electroencephalographic abnormalities that have previously been associated with poor outcomes.

Methods

We conducted a multicenter, international retrospective review of patients hospitalized in the ICUs at L'Enfant-Jésus Hospital, Quebec City, Quebec, Canada; Lausanne University Hospital and Lausanne University, Lausanne, Switzerland; and Mayo Clinic Hospital, Rochester, Minnesota. The Bureau de l'éthique de la recherche du CHU de Québec (Quebec), Commission cantonale (VD) d'éthique de la recherche sur l'être humain (Lausanne), and Mayo Clinic Institutional Review Board (Rochester) approved the study protocol.

This study comprised consecutive patients admitted to the participating centers from October 1, 2012, through September 30, 2014. Data analysis was performed from January 16, 2015, to June 15, 2015. Consecutive patients 18 years and older with an altered level or content of consciousness (Glasgow Coma Scale score <15 or positive Confusion Assessment Method for the ICU score) admitted to an ICU for any diagnosis who underwent routine EEG or continuous EEG monitoring to exclude nonconvulsive seizures were included in the study.

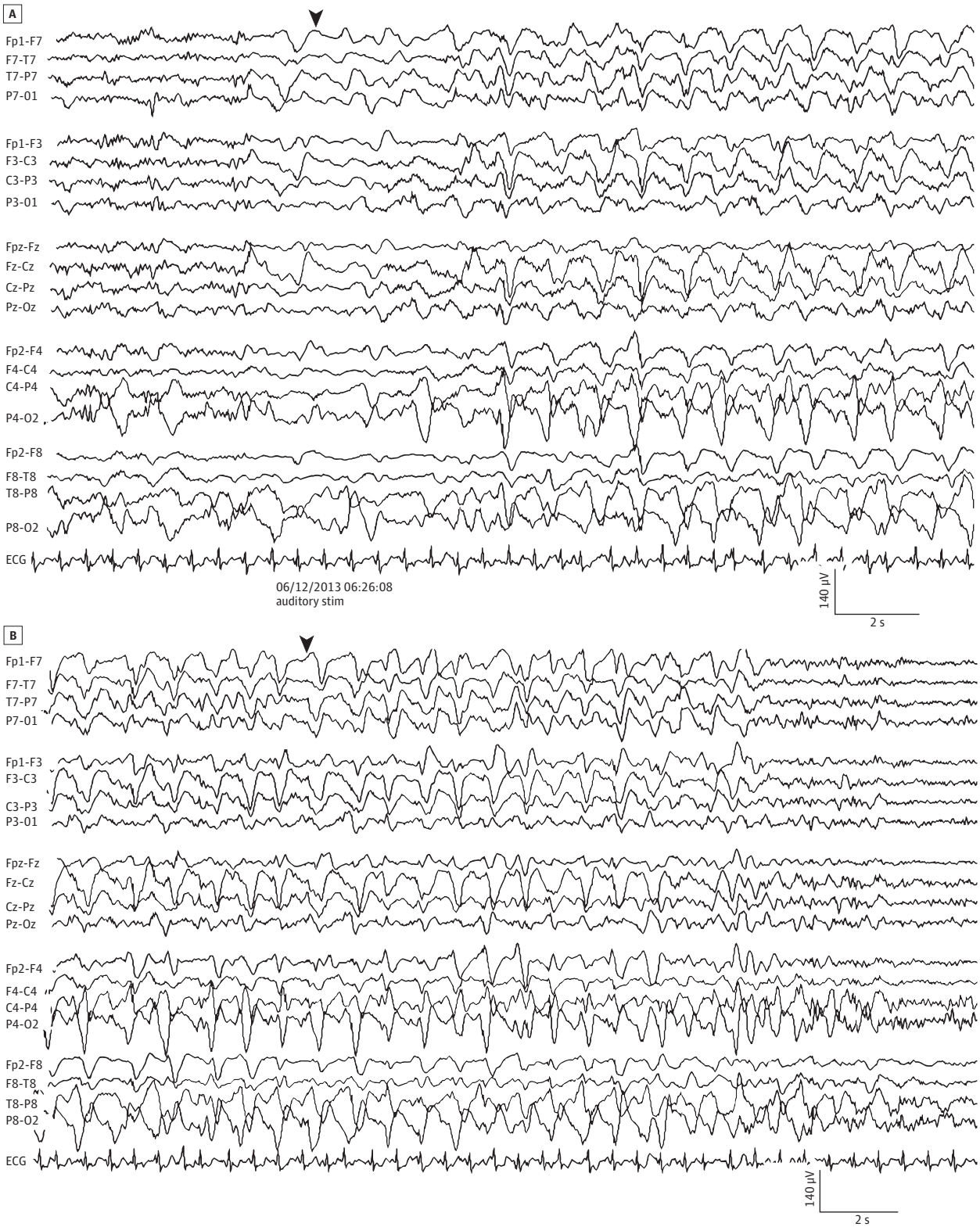
Data collected included age, sex, history of epilepsy, primary admitting diagnosis, medications administered during the EEG recording (including antiepileptics and anesthetics), length of hospitalization, clinical or electrographic seizures during hospitalization, and Glasgow Outcome Scale score[11] at the time of hospital discharge.

The EEG recordings were obtained using the international 10-20 system and were reviewed for the best background activity (alpha, beta, theta, delta, or burst suppression or discontinuous patterns), presence of sporadic sharp waves and PDs (the latter comprising generalized PDs without triphasic morphologic features and lateralized PDs), generalized PDs with triphasic morphologic features, reactivity to stimulation, and presence of SIRPIDs. Reactivity to visual, auditory, and noxious stimulation was consistently tested during all recordings. SIRPIDs were defined as rhythmic, periodic, or ictal discharges that were consistently induced by alerting stimuli, such as noises, sternal rub, physical examination, suctioning, turning, and other activities related to patient care.[1] We considered a pattern to be periodic when it consisted of discharges (sharp waves, spikes, polyspikes, or sharply contoured delta waves) recurring at regular or nearly regular intervals with an identifiable interdischarge interval. If the pattern became continuous, with no separation between individual discharges, the pattern was considered rhythmic. In addition, the minimum, maximum, and mean duration of SIRPIDs and the type of stimulus that elicited the response were noted.

The American Clinical Neurophysiology Society's 2012 Guidelines[12] recommend classifying SIRPIDS under the rubric of stimulus-induced activity and categorizing the type of stimulus-induced discharges. We categorized SIRPIDs identified in our study as rhythmic delta activity, PDs, or seizure discharges. The numbers of each subcategory of SIRPID type were too small to assess their significance individually. As a result, all SIRPID types were considered in aggregate for statistical analysis purposes.

Descriptive summaries are reported as mean (SD) or median (interquartile range [IQR]) for continuous variables and as frequencies and percentages for categorical variables. Categorical variables were compared using the χ^2 test or Fisher exact test, and continuous variables were compared using the 2-sample *t* test or Wilcoxon rank sum test, as appropriate. Associations between binary outcomes, such as SIRPIDs (yes, no), and other predictor variables were

Figure. Stimulus-Induced Rhythmic, Periodic, or Ictal Discharges (SIRPIDs)



A 64-year-old comatose woman with seizures after right subdural hematoma evacuation. Baseline electroencephalogram shows right posterior breach rhythm. Top, Auditory stimulus results in onset of generalized rhythmic delta activity with triphasic morphologic features. Bottom, Consecutive epoch shows termination of rhythmic SIRPIDs.

Table 1. Variables Associated With SIRPIDs on Univariate Analysis[a]

Variable	SIRPIDs (n = 43)	No SIRPIDs (n = 373)	*P* Value
Age, median (IQR), y	64.0 (52-78)	59.0 (45-70)	.03
Anoxic brain injury	16 (37.2)	85 (22.8)	.06
In-hospital mortality	18 (41.9)	86 (23.1)	.01
Generalized PDs with triphasic morphologic features	14 (32.6)	58 (15.5)	.01
Sporadic sharp waves and PDs	25 (58.1)	83 (22.3)	<.001
Absence of EEG reactivity	11 (25.6)	56 (15.0)	.08
Burst suppression or discontinuous patterns	2 (4.7)	34 (9.1)	.56
PDs alone	15 (34.9)	43 (11.5)	<.001
History of epilepsy	2 (4.7)	41 (11.0)	.29
Clinical seizure during hospitalization	12 (27.9)	99 (26.5)	.85
Electrographic seizure	13 (30.2)	30 (8.0)	<.001
Use of antiepileptic medication	34 (79.1)	185 (49.6)	<.001
Use of anesthetic medication	25 (58.1)	197 (52.8)	.52

Abbreviations: EEG, electroencephalographic; IQR, interquartile range; PD, periodic discharge; SIRPIDs, stimulus-induced rhythmic, periodic, or ictal discharges.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

Table 2. Variables Associated With SIRPIDs on Multivariate Analysis

Variable	OR (95% CI)	*P* Value
Anoxic brain injury	3.80 (1.73-8.33)	<.001
Use of antiepileptic medications	3.24 (1.31-8.00)	.01
Electrographic seizure	2.85 (1.13-7.19)	.03
Generalized PDs with triphasic morphologic features	3.66 (1.67-8.02)	.001
Sporadic sharp waves and PDs	2.59 (1.13-5.92)	.02

Abbreviations: OR, odds ratio; PD, periodic discharge; SIRPIDs, stimulus-induced rhythmic, periodic, or ictal discharges.

assessed using univariate and multivariate logistic regression. Variables with $P < .10$ were considered candidate variables for multivariate model building. The magnitude of association was reported as odds ratio (95% CI). The prediction ability of the final model was quantified using the area under the receiver operating characteristic curve. All tests were 2-sided, and $P < .05$ was considered statistically significant. Analysis was performed using SAS statistical software, version 9.3 (SAS Institute Inc).

Results

A total of 416 patients were included in the final analysis. The median age of the patients was 60 years (IQR, 46-71 years), and 252 (60.6%) were male. Sixty-six patients were enrolled from Quebec, 205 from Lausanne, and 145 from Rochester. Continuous (prolonged) EEG recordings were available in 170 patients (40.9%), whereas short-term EEG recordings were available in 246 (59.1%). One hundred one patients (24.3%) had previous anoxic brain injury. Forty-three patients (10.3%) had a prior history of epilepsy, and 111 patients (26.7%) had a clinical seizure during their hospitalization. Abnormalities on EEG testing were recorded in 394 patients (94.7%). Background revealed normal alpha activity in 82 patients (19.7%) and burst suppression or discontinuous patterns in 36 patients (8.7%). Periodic discharges without triphasic morphologic features were seen in 58 patients (13.9%), and PDs with triphasic morphologic features were seen in 72 patients (17.3%). Patients were hospitalized for a median of 15 days (IQR, 7.0-29.5 days).

SIRPIDs were identified in 43 patients (10.3%). The incidence of SIRPIDs was not significantly different among the study sites (8.8%, 15.2%, and 10.3% in Quebec, Lausanne, and Rochester, respectively; $P = .34$). The proportion of patients with SIRPIDs identified on short-term EEG recordings was not significantly different from those with SIRPIDs identified with continuous monitoring (20 [46.5%] vs 23 [53.5%], $P = .10$). Among patients with SIRPIDs, only 7 (16.3%) had normal alpha background activity. Electroencephalographic background reactivity (other than SIRPID response) was present in 32 patients (74.4%) with SIRPIDs. The inciting stimulus in SIRPID cases was noxious in most cases (90.7%). SIRPIDs persisted for a mean of 60 seconds (IQR, 4.5-240.0 seconds) and were characterized as periodic in 23 patients (53.5%), rhythmic in 16 patients (37.2%), and ictal in 4 patients (9.3%). Twelve patients with SIRPIDs had a clinical seizure while hospitalized.

Multiple factors correlated with the presence of SIRPIDs on univariate analyses (**Table 1**). On multivariate analysis, anoxic brain injury ($P < .001$), use of antiepileptic medications ($P = .01$), electrographic seizures ($P = .03$), presence of generalized PDs with triphasic morphologic features ($P = .001$), and sporadic sharp waves and nontriphasic PDs ($P = .02$) retained a significant association with SIRPIDs (**Table 2**).

The presence and shorter duration of SIRPIDs, among other variables, were associated with mortality ($P = .01$) on univariate analysis (**Table 3**). A history of epilepsy ($P = .04$) was inversely associated with mortality. On multivariate analysis (**Table 4**), older age ($P = .005$), anoxic brain injury ($P < .001$), and absence of EEG reactivity ($P < .001$) remained independently associated with in-hospital mortality, but SIRPIDs were not.

Discussion

This observational and retrospective study of patients with encephalopathy in the ICU who underwent EEG recordings found

Table 3. Variables Associated With In-Hospital Mortality on Univariate Analysis[a]

Variable	Died (n = 104)	Survived (n = 312)	*P* Value
Age, median (IQR), y	63.5 (55-76)	58.0 (43-69)	.001
Anoxic brain injury	49 (47.1)	52 (16.7)	<.001
Presence of SIRPIDs	18 (17.3)	25 (8.0)	.01
Duration of SIRPIDs, median (IQR), s	5.3 (2-60)	142 (40-345)	.002
Maximum SIRPID duration, median (IQR), s	5.5 (2-180)	275 (30-900)	<.001
Minimum SIRPID duration, median (IQR), s	6 (2-15)	39 (14-64)	.004
Generalized PDs with triphasic morphologic features	22 (21.2)	50 (16.0)	.23
Sporadic sharp waves and PDs	40 (38.5)	68 (21.8)	.001
Absence of EEG reactivity	44 (42.3)	23 (7.4)	<.001
Burst suppression or discontinuous patterns	22 (21.2)	14 (4.5)	<.001
PDs alone	17 (16.3)	41 (13.1)	.42
History of epilepsy	5 (4.8)	38 (12.2)	.04
Clinical seizure during hospitalization	16 (15.4)	95 (30.4)	.003
Electrographic seizure	11 (10.6)	32 (10.3)	.66
Use of antiepileptic medication	55 (52.9)	164 (52.6)	>.99
Use of anesthetic medication	63 (60.6)	159 (51.0)	.11

Abbreviations: EEG, electroencephalographic; IQR, interquartile range; PD, periodic discharge; SIRPIDs, stimulus-induced rhythmic, periodic, or ictal discharges.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

that in-hospital mortality was associated with older age, anoxic brain injury, and absent reactivity on EEG testing but not with the presence of SIRPIDs. SIRPIDs were more common in patients who died in the hospital (17.3% vs 8.0% in survivors), but this association was not significant when adjusted for other prognostic factors.

In our population, SIRPIDs were present in 43 patients (10.3%). Distinct epileptiform abnormalities commonly cooccurred with SIRPIDs, which may indicate an epileptogenic potential of SIRPIDs. Antiepileptic therapy is commonly used in patients with SIRPIDs and discharges considered epileptiform, but the utility of suppressing SIRPIDs in these patients remains uncertain.

The duration of SIRPIDs was shorter in patients who died in the hospital compared with those who survived. This finding argues against the notion that these EEG features may represent an ictal pattern because one might anticipate higher mortality and other poor outcomes to be associated with a prolonged duration of discharges despite treatment, along the lines of refractory status epilepticus.[13-15] It is probable that a spectrum of neuronal injury is responsible for the neurophysiologic changes of SIRPIDs, which may be considered less severe or potentially reversible in some circumstances.[2] This finding may be reflected by the different types of SIRPIDs (ie, rhythmic, periodic, or ictal).

Patients with a preexisting diagnosis of epilepsy or an in-hospital seizure were less likely to die in the hospital in our cohort. Previous studies[16,17] have found that patients with known epilepsy have improved outcomes in status epilepticus compared with patients with acute disease, and, consequently, a previous diagnosis of epilepsy has been incorporated into status epilepticus severity and mortality scales as a favorable factor relative to acute disease. The improved survival noted in patients with clinical seizures is more surprising because these seizures were not solely seen in patients with preexisting epilepsy. It is possible that the presence of seizures led to a more aggressive antiepileptic treatment, or, alternatively, patients with seizures may have been encephalopathic because of a postictal state rather than because of non–seizure-related causes associated with worse prognosis. Electrographic seizures were not associated with mortality, whereas epileptiform discharges were. This finding was somewhat unexpected, but a reasonable explanation could be that a greater preservation of neuronal circuitry is necessary for electrographic seizures to occur; hence, seizures may indicate less severe cerebral injury.

Table 4. Variables Associated With In-Hospital Mortality on Multivariate Analysis

Variable	OR (95% CI)	*P* Value
Older age	1.02 (1.01-1.04)	.005
Anoxic brain injury	3.49 (1.96-6.21)	<.001
Burst suppression or discontinuous patterns	1.36 (0.55-3.36)	.51
SIRPIDs	1.73 (0.79-3.78)	.17
Absence of EEG reactivity	8.14 (4.20-15.79)	<.001

Abbreviations: OR, odds ratio; EEG, electroencephalographic; SIRPIDs, stimulus-induced rhythmic, periodic, or ictal discharges.

Our study confirms the importance of several prognostic factors, most notably the lack of EEG reactivity. Although any significantly abnormal EEG findings may be prognostically unfavorable, the ability to sustain EEG reactivity after stimulation, even when aberrant, indicates less severe cerebral injury and, consequently, an improved chance of survival. This finding aligns with the observation that patients with normothermia with preserved EEG reactivity have more favorable short-term outcome.[18]

This study has limitations. The observational and retrospective nature of data collection made the degree of functional impairment difficult to fully characterize in some cases;

thus, we opted to include in-hospital mortality as the only clinical end point. Given the 3-site design and multiple epileptologists (D.B.B., A.O.R., M.S., and J.W.B.) who reviewed the EEG recordings, there may have been variability in the interpretation of EEG findings; however, no significant difference in the incidence of SIRPIDs among sites was noted. The type of EEG recording obtained (short-term vs continuous) may have resulted in some episodes of SIRPIDs being overlooked if only a short-term recording was performed. Given the small number of patients who experienced SIRPIDs, further evaluation of the clinical and prognostic implications of each subtype of SIRPID was unable to be confidently completed.

Conclusions

SIRPIDs occurred in 43 patients (10.3%) with encephalopathy in the ICU examined with EEG recordings. Generally, SIRPIDs were accompanied by other EEG abnormalities, including electrographic seizures and epileptiform discharges. Although SIRPIDs were more common in patients who did not survive the hospitalization, their presence was not independently associated with in-hospital mortality. Older patients, those with anoxic brain injury, and those without EEG reactivity were more likely to die in the hospital.

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Study concept and design: Braksick, Burkholder, Britton, Rabinstein.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Braksick, Burkholder.
Critical revision of the manuscript for important intellectual content: Tsetsou, Martineau, Mandrekar, Rossetti, Savard, Britton, Rabinstein.
Statistical analysis: Braksick, Mandrekar.
Administrative, technical, or material support: Savard.
Study supervision: Rabinstein.

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