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Reactive EEG Patterns in Pediatric Coma

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This study was designed to determine whether the observed reactive electroencephalographic patterns in comatose children were associated with a better outcome. All electroencephalograms performed in comatose children aged 2 months to 18 years during the period 1996-2003 were retrospectively analyzed and classified according to modified Young's classification. Reactivity to painful/auditory stimuli and passive eye closure (at least two modalities) was checked in all electroencephalograms. The clinical outcome at 1 year or during the last clinic/inpatient follow-up was scored according to the Pediatric Cerebral and Overall Performance Category Scale. Outcomes were then compared using Fisher exact test and the Mann-Whitney test. Thirty-three patients had electroencephalography within 72 hours after the onset of coma. Fourteen of 33 electroencephalograms revealed reactive patterns. Outcome was unfavorable in 4 (28.6%) of these patients. Three children had no residual neurologic impairment. Among the 19 children with nonreactive electroencephalogram, 13 (65%) had unfavorable outcome, which included 10 deaths. All the survivors had residual neurologic impairment. Outcome was better in children with reactive electroencephalographic patterns (Fisher exact test; $P = 0.023$). Comatose children with reactive electroencephalographic patterns have better clinical outcome in terms of morbidity and mortality. A careful assessment of electroencephalographic reactive patterns in all comatose children is required for better understanding of the clinical outcome. **© 2005 by Elsevier Inc. All rights reserved.**

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Introduction

Electroencephalography is a helpful neurologic tool for diagnosis, treatment guidance, and prognostication of comatose children. The etiologies with differing inherent prognostic implications may present with a similar electroencephalographic pattern in coma. Central nervous system depressants can produce significant suppression of the background, burst-suppression, or alpha coma pattern. Hence, it is difficult to predict the outcome based on electroencephalographic pattern alone [1,2]. To date, there is sufficient evidence from adult studies that reactive electroencephalographic patterns are associated with a better clinical outcome irrespective of the etiology [3]. Also, one study in comatose neonates had demonstrated that reactive burst-suppression pattern in electroencephalography was associated with a better prognosis [4]. Therefore, the objective of this study was to determine whether reactive electroencephalographic patterns in comatose children were associated with a better clinical outcome.

Methods

Patients

All children who had an electroencephalographic recording within 72 hours after the onset of coma were included. Cases were initially identified from the electroencephalographic database. A data abstraction form was designed to gather the clinical details, including age and sex of patients, onset and cause of coma, drug treatment, time of electroencephalograms, neuroimaging findings, follow-up, and outcome. Children with preexisting developmental delay and neurologic deficits were excluded from the study. Modified James' Glasgow Coma Scale score was used to define coma [5]. This study was approved by the research ethics board of the Hospital for Sick Children.

Electroencephalographic Recordings

First electroencephalographic recording performed within 72 hours in comatose children between the ages of 2 months and 18 years at the

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Hospital for Sick Children, Toronto during the period July 1996 to June 2003 were analyzed retrospectively. Electroencephalograms were recorded using the International 10-20-electrode placement system with 10-mm Grass Gold plated disc electrodes and paste application. Electrode impedance ranged from 1000 to 5000 ohms. All electroencephalograms were recorded using either Stellate-Rhythm version 9.0 digital software (Montreal, Quebec) before 1999 or XLTEK-Neuroworks version 3.3 digital software (Oakville, Ontario) from 1999 onwards. Thirty-minute digital recordings were made at a sampling rate of 200 Hz with an open-ended band pass using Pz' electrode (which is located 1 cm posterior to Pz) as a reference. The minimum vertical resolution used was 12 bits or better. All our electroencephalographic recordings conformed to the Canadian electroencephalographic standards [6].

Test for Electroencephalographic Reactive Patterns

All patients were tested for electroencephalographic reactivity by at least two of the three modalities. Painful stimulus was performed by either pinching the ear lobe or pressing the nail bed of the thumb. Auditory stimulus was produced by a loud noise close to the patient's ear (clapping). Sustained passive eye closure and opening lasted for a minimum of 10 seconds. All these stimulating procedures were documented twice.

Variables Evaluated

A staff neurophysiologist (M.A.C.), with no knowledge of the clinical data, analyzed all electroencephalographic recordings. Reactive electroencephalographic pattern was defined as a change in the frequency or voltage of the background activity, with a precise time locked correlation to the stimulation. Young's classification [7] was used to categorize the electroencephalographic pattern. Subcategorizing rhythmic patterns (original category IV) to "reactive" and "nonreactive" groups modified the Young's classification. The alpha, beta, spindle, and theta frequencies that persisted for more than 50% of the record were defined as rhythmic coma patterns.

Clinical Outcome Score System

Clinical outcome was scored from 1 to 6 according to the Pediatric Cerebral and Overall Performance Category Scale (PCOPCS) (Scores 1-6; 1–normal, 2–mild disability, 3–moderate disability, 4–severe disability, 5–coma or vegetative state, 6–brain death) [8]. The PCOPCS score was ascertained by taking the clinical data as recorded by the treating physician at the last available follow-up or at 1 year (whichever was earlier). PCOPCS outcome was "favorable" when the score was 3 or less. PCOPCS outcome was "unfavorable" if the score was higher than 3.

Statistical Analysis

Fisher exact test was used to determine whether children with reactive electroencephalographic pattern had a favorable outcome and Mann-Whitney rank-sum test to determine whether reactive electroencephalographic patterns were associated with a lower PCOPCS score, with the probability value of $P < 0.05$ chosen as an index of statistical significance.

Results

Prevalence of Reactive Coma Patterns

Sixty-eight comatose patients were identified during the study period. Thirty children were excluded from analysis owing to insufficient clinical information, poor coma scoring, or preexisting neurologic deficits. Thirty-eight patients satisfied the clinical inclusion criteria. However, only 33 children (19 males and 14 females) had at least one electroencephalogram performed within 72 hours. Age ranged from 2 months to 17 years (mean 8.06 ± 5.1 years). Etiology of coma was: hypoxic encephalopathy (n = 9), head injury (n = 5), metabolic (n = 3), infection (n = 8), raised intracranial pressure (n = 3; all with congenital hydrocephalus and blocked shunt), status epilepticus (n = 3), and stroke (n = 2). The most common electroencephalographic pattern was polymorphic delta frequency (n = 18). Other electroencephalographic patterns included alpha coma (n = 5), beta coma (n = 4), spindle coma (n = 4), and burst-suppression (n = 2).

Clinical Outcome

A reactive electroencephalographic pattern (Fig 1) was detected in 14 children (42%). Table 1 illustrates the clinical characteristics of children with reactive and nonreactive electroencephalographic patterns. Electroencephalographic reactivity was more common with rhythmic coma patterns (9/13) than with polymorphic delta frequency pattern (5/18). All survivors had a mean follow-up of 10.9 months. Clinical outcome was unfavorable in only 4 (28.6%) patients with reactive electroencephalographic pattern. Three children had no residual neurologic impairment at 1 year. Of 19 children with nonreactive electroencephalogram (Fig 2), 13 (65%) had unfavorable outcome, including mortalities (n = 10). All survivors (n = 9) had residual neurologic impairment. Children with reactive electroencephalographic patterns were likely to have a favorable outcome (n = 14) (Fisher exact test; $P = 0.023$). Reactive electroencephalographic pattern was associated with a lower PCOPCS score on follow-up (Mann-Whitney $P = 0.002$).

Discussion

Although electroencephalography is an important neurologic tool for the investigation of a comatose child, its usefulness in predicting the clinical outcome had been limited. Part of this limitation was historically due to the lack of uniformity in the definition of different electroencephalographic patterns. Also, etiologies with differing inherent prognostic implications often presented with the same electroencephalographic pattern in coma. And furthermore, drugs that are administered for the treatment of the underlying condition or associated seizures could modify the electroencephalographic pattern significantly. Hence, to predict the clinical outcome based on the electroencephalographic pattern alone was difficult [1,2]. Etiology and outcome of alpha coma, spindle coma, beta coma, and theta coma patterns (collectively termed as rhythmic coma patterns) are similar [9-12]. All the 19 children with alpha coma pattern reported in literature had nonreactive electroencephalography. Ten (52.6%) children died, five had normal neurologic status or

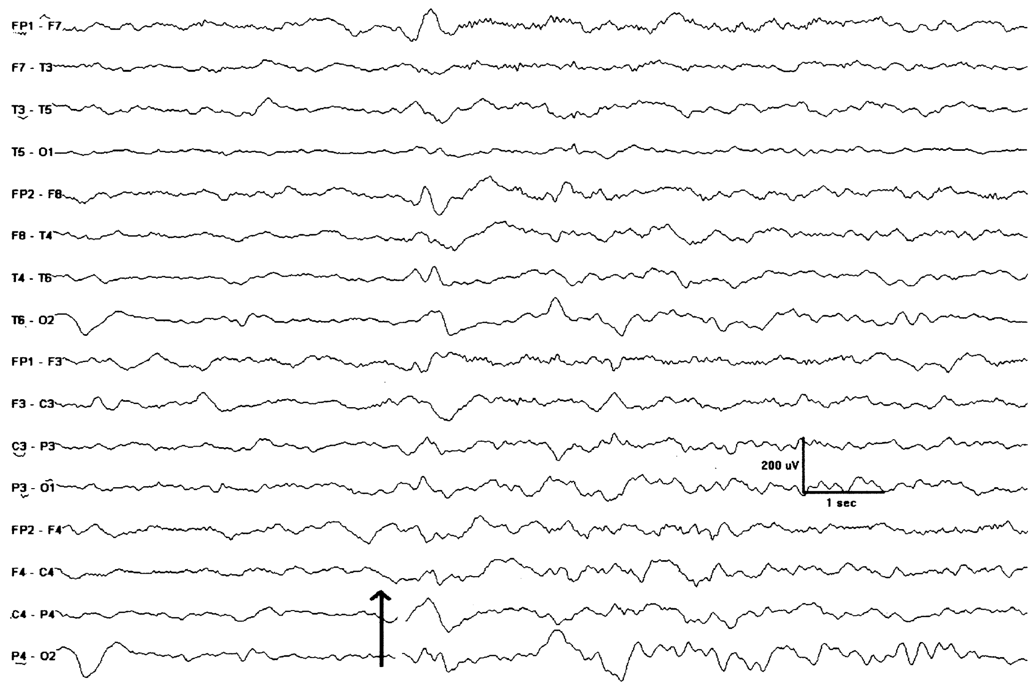

Figure 1. Reactive coma pattern depicted on an anterior-posterior bipolar montage recorded on the first day of hospital admission of an 11-year-old comatose male. Electroencephalogram disclosed diffuse 50-µV polymorphic delta activity at 1 to 1.5 Hz with intermingled random theta activity at 4 to 5 Hz. During passive eye closure (arrow) there was a twofold increase in amplitude of the polymorphic delta activity and theta activity and more overt and frequent 100-µV sharply countered slow waves over the occipital derivations.

returned to pre-event status, and four had severe neurologic deficits [9-12]. Six of the 10 children with cardiorespiratory arrest died. Only one child with cardiorespiratory arrest had a normal neurologic outcome. Similarly, burst-suppression pattern and suppression were not uncommon in drug intoxication. Prognosis was good in this situation irrespective of the electroencephalographic pattern. However, if the etiology was hypoxic coma, these patterns denoted a bad prognosis [1].

Previous studies focused mostly on the prognostic value of electroencephalographic patterns of pediatric coma but not specifically on electroencephalographic reactive pat-

Table 1. Comparison of children with reactive and nonreactive EEG patterns

Variable	Reactive EEG Group	Nonreactive EEG Group
Age in years (mean)	9.3	7.2
Etiology		
Hypoxic encephalopathy	4	5
Head injury	2	3
Metabolic	1	2
Infection	3	5
Raised intracranial pressure	2	1
Status epilepticus	2	1
Stroke	0	2
Mean coma score	7	6.9
EEG pattern		
Spindle coma	3	1
Alpha coma	3	2
Beta coma	3	1
Delta frequency	5	13
Burst-suppression	—	2
Outcome		
Mean follow-up* (for survivors)	10.9 months (± 2.08)	11.2 months (± 1.3)
Mean outcome score	3.7	4.6
Unfavorable outcome	4	13
Death	4	10
Favorable outcome	10	6
Normal on follow-up	3	0

* This is the mean follow-up of survivors used for assigning outcome score.

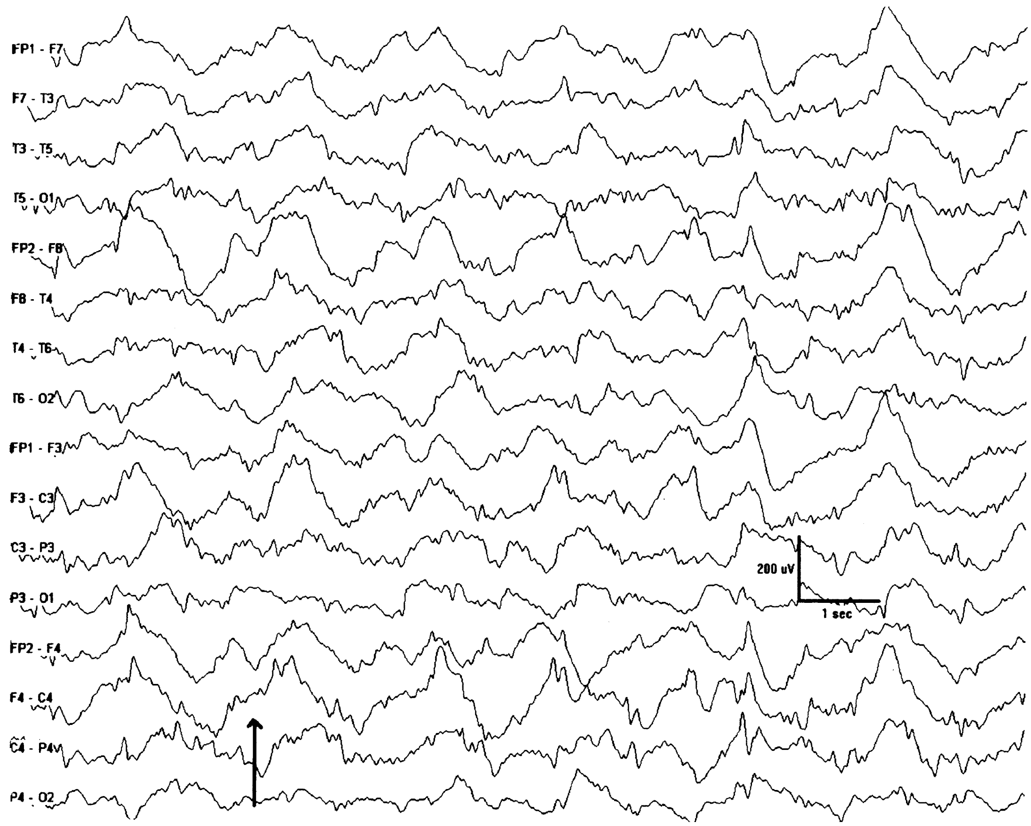

Figure 2. Nonreactive coma pattern disclosed on an anterior-posterior bipolar montage recorded on the second day of hospital admission of a 10-year-old comatose male. Electroencephalogram revealed diffuse 200-μV polymorphic delta activity at 0.5 to 1 Hz with intermingled irregular 35- to 50-μV random 8- to 9-Hz alpha and theta waves at 4 to 7 Hz with frequent bilateral fronto-temporal sharply countered and biphasic high-amplitude slow waves. During painful stimulation (arrow), there were no changes in amplitude or frequency of the described background activity.

terns [13-16]. For instance, burst-suppression, alpha-like activity, low amplitude, and suppression (not related to drug) were associated with poor outcome in a study of 54 comatose children [14]. Similarly, polymorphic delta activity was the most frequently observed electroencephalographic pattern in 17 comatose children. Eleven children had an unfavorable outcome with either mortality or severe neurologic deficit (follow-up: 1-6 months). Isoelectric electroencephalographic and burst-suppression patterns were associated with unfavorable outcome as well. Two children manifested a spindle coma pattern and had a favorable outcome after a drug overdose or metabolic condition [15]. A prospective study on 57 comatose children with hypoxic-ischemic encephalopathy reported that a discontinuous electroencephalogram and presence of epileptiform discharges were associated with an unfavorable outcome (positive predictive value of 100% for two criteria). Electroencephalographic reactivity was tested in 42 comatose children. Nonreactive electroencephalographic pattern was associated with unfavorable outcome with a 96% positive predictive value (follow-up for 2 years). The authors did not provide the number of children with reactive patterns [16]. The definition of electroencephalographic reactive patterns did not include the current practice [17-19].

There is one study that looked into the prognostic value of reactive burst-suppression pattern in newborns. All the neonates (n = 16) with a nonreactive burst-suppression pattern had poor outcome (11 mortalities and 5 severe or moderate impairment) at follow-up. Three of 16 (18.6%) had a reactive burst-suppression pattern, and they became neurologically normal or mildly impaired (follow-up: 3-9 years) [4].

In the present study, 71.4% of children with a reactive electroencephalographic pattern had a favorable outcome, including three children who had normal neurologic outcome on follow-up. Most of the children with a nonreactive electroencephalogram had an unfavorable outcome (65%), which included 10 deaths. In the nonreactive electroencephalographic pattern group, no child became neurologically normal on follow-up. Lack of reactivity on the electroencephalogram had a positive predictive value of 52.6% (95% confidence interval: 30.2-75.1%) for mortality. Because these two groups were matched for age, etiology, mean coma score, and electroencephalographic patterns, we reasoned that the electroencephalographic reactivity might be an independent predictor for prognosis. To support this notion, there are few studies in adult comatose patients that had documented better clinical outcome associated with reactive electroencephalographic patterns [17,18]. Thirty-six of 50 patients with severe head injury manifested a reactive electroencephalographic pattern. Thirty-three (91.6%) patients had a good outcome; 13 patients (92.9%) with nonreactive electroencephalogram had a bad outcome (9 deaths) [17].

In another study of 14 adult patients with postanoxic alpha coma, all patients with nonreactive alpha coma died and 3 of 5 patients with reactive alpha coma survived [18].

Although neurologic improvement in children had been documented for 1.5 to 5 years since the onset of coma, we used a short-term follow-up of 1 year (maximum) for assigning the PCOPCS score. Many patients in the present study had a clinical follow-up of more than 1 year. Seven children (4 in the nonreactive group and 3 in the reactive group) had only less than 1 year follow-up. PCOPCS is a well-validated scale in pediatric practice [8,16,20]. However; it is not validated for long-term outcome [8]. Hence, for statistical analysis we used the PCOPCS score at 1 year or the last clinic visit (if it was before 1 year). A previous study from our institution on comatose children used 6-month follow-up [21].

The neurophysiologic basis for a better clinical outcome associated with electroencephalographic reactivity is not clearly understood. Electroencephalographic reactive patterns may represent a minimally preserved function of the reticular activating system [17]. Our data suggest that electroencephalographic reactivity should be tested in all comatose children for prognostic purposes. As the testing modalities have different sensory input and strength, we used at least two modalities in each patient. We acknowledge, however, that there are clinical conditions, such as suspected raised intracranial pressure, where less intense nociceptive stimulation is preferred, to avoid possible further rise in intracranial pressure [19]; but auditory stimulation or sustained passive eye closure and opening might be an option in these cases.

Conclusion

The data from this study indicate that reactive electroencephalographic patterns in comatose children are associated with a better clinical outcome. Electroencephalographic reactive pattern may represent an independent prognostic predictor, irrespective of the etiology, coma score, and electroencephalographic pattern. Routine testing for electroencephalographic reactivity in all comatose children is warranted.

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References

[1] **Shewmon** DA. Coma prognosis in children. Part I: Definitional and methodological challenges. J Clin Neurophysiol 2000;17:457-66.

[2] **Shewmon** DA. Coma prognosis in children. Part II: Clinical application. J Clin Neurophysiol 2000;17:467-72.

[3] **Young** GB, Wang JT, Connolly JF. Prognostic determination in anoxic-ischemic and traumatic encephalopathies. J Clin Neurophysiol 2004;21:379-90.

[4] **Douglass** LM, Wu JY, Rosman NP, Stafstrom CE. Burst suppression electroencephalogram pattern in the newborn: Predicting the outcome. J Child Neurol 2002;17:403-8.

[5] **Tatman** A, Warren A, Williams A, Powell JE, Whitehouse W. Development of a modified paediatric coma scale in intensive care clinical practice. Arch Dis Child 1997;77:519-21.

[6] **Task Force of the Canadian Society of Clinical Neurophysiologists.** Minimal standards for electroencephalography in Canada. Can J Neurol Sci 2002;29:216-20.

[7] **Young** GB, McLachlan RS, Kreeft JH, Demelo JD. An electroencephalographic classification for coma. Can J Neurol Sci 1997;24:320-5.

[8] **Fiser** DH. Assessing the outcome of pediatric intensive care. J Pediatr 1992;121:68-74.

[9] **Young** GB, Blume WT, Campbell VM, et al. Alpha, theta and alpha-theta coma: A clinical outcome study utilizing serial recordings. Electroencephalogr Clin Neurophysiol 1994;91:93-9.

[10] **Horton** EJ, Goldie WD, Baram TZ. Rhythmic coma in children. J Child Neurol 1990;5:242-7.

[11] **Frisher** S, Herishanu Y. Mu and alpha rhythm in comatose children. Childs Nerv Syst 1985;1:208-10.

[12] **Sarma** GR, Kumar A, Roy AK, Pinheiro L. Post-cardiorespiratory arrest beta-alpha coma: an unusual electroencephalographic phenomenon. Neurol India 2003;51:266-8.

[13] **Mewasingh** LD, Christophe C, Fonteyne C, et al. Predictive value of electrophysiology in children with hypoxic coma. Pediatr Neurol 2003;28:178-83.

[14] **Johnston** B, Seshia SS. Prediction of outcome in non-traumatic coma in childhood. Acta Neurol Scand 1984;69:417-27.

[15] **Strickbine-Van Reet** P, Glaze DG, Hrachovy RA. A preliminary prospective neurophysiological study of coma in children. Am J Dis Child 1984;138:492-5.

[16] **Mandel** R, Martinot A, Delepoulle F, et al. Prediction of outcome after hypoxic-ischemic encephalopathy: A prospective clinical and electrophysiologic study. J Pediatr 2002;141:45-50.

[17] **Gutling** E, Gonser A, Imhof HG, Landis T. EEG reactivity in the prognosis of severe head injury. Neurology 1995;45:915-8.

[18] **Kaplan** PW, Genoud D, Ho TW, Jallon P. Etiology, neurologic correlations, and prognosis in alpha coma. Clin Neurophysiol 1999;110:205-13.

[19] **Young** GB. The EEG in coma. J Clin Neurophysiol 2000;17:473-85.

[20] **Carter** BG, Taylor A, Butt W. Severe brain injury in children: Long-term outcome and its prediction using somatosensory evoked potentials (SEPs). Intensive Care Med 1999;25:722-8.

[21] **Beca** J, Cox PN, Taylor MJ, et al. Somatosensory evoked potentials for prediction of outcome in acute severe brain injury. J Pediatr 1995;126:126:44-9.