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Original article

Neonatal seizures: characteristics of EEG ictal activity in preterm and fullterm infants

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Abstract

The neonatal EEG remains one of oldest, yet most valuable, diagnostic and prognostic tests in neonates. The goals of this study were to determine the relationships between the morphology, frequency, and distribution of ictal discharges in the neonatal EEG with age, EEG background activity, and etiology. A total of 156 ictal events were evaluated in 11 preterm (PT) and 25 fullterm (FT) infants. Most of the infants had severe abnormalities of background activity although ictal discharges occurred on both normal and abnormal backgrounds. There was a trend for a closer relationship between behavioral changes during the electroencephalographic seizure when the background activity was normal or moderately abnormal than when background activity was severely abnormal. In both PT and FT infants, the most common site of seizure origin was the temporal lobe. FT infants commonly had sharp waves, spikes, sharp and slow waves, and spike and slow waves at the onset of the ictus while rhythmic delta activity was most common in the PT infants. PT infants typically had a regional onset to the ictus whereas FT infants most frequently had a focal onset. Duration of the ictal events was similar in PT and FT infants and a change in morphology or frequency of the discharges was common during propagation of the ictal discharges in both age groups. There was not a clear relationship between onset, morphology, frequency, or propagation patterns and etiology in either the PT or FT infants. Our results demonstrate that while the type of ictal discharge is related to gestational age, there is a rich variety in the onset, morphology, and frequency of the ictal discharges in both PT and FT infants and that neonatal ictal patterns lack a close correlation with underlying pathology.

Keywords: Epilepsy; Electroencephalography; Antiepileptic drugs

1. Introduction

Seizures occur more frequently in the neonatal period than at any other time in life [1,2]. Seizures usually reflect important central nervous system insults; their recognition is necessary because they are associated with a high morbidity and mortality rate [3–6]. The EEG remains the standard test for distinguishing epileptic seizures from non-epileptic behavior and detecting subclinical seizure activity [1,7,8].

There are striking differences between seizures in neonates and those of older patients in ictal EEG patterns and their correlation with clinical symptoms and pathology. For example, in the neonatal period, ictal discharges are frequently focal in metabolic disorders (e.g. in hypocalcemic or hypoglycemic seizures) as well as structural lesions (e.g. infarction) [9]. Seizures may have an erratic evolution, shifting from one area to another regardless of whether the pathological process is diffuse or more localized [9]. Neonatal ictal patterns may vary in frequency, morphology, duration, or propagation at different times during a single event or from one seizure to the next [10–12].

While the neonatal EEG is of enormous value in differentiating seizures from non-epileptic events and providing prognostic information, the relationship between age and electrographic features of the ictal events has not been well studied. Since there are substantial maturational changes in the neonate during the last trimester we wished to compare the electrographic characteristics of neonatal seizures in PT and FT infants to see if there are age-related differences in EEG ictal onset, morphology, frequency, propagation, and duration. A second goal of the study was to

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determine if EEG ictal characteristics were related to etiology of the seizures.

2. Material and methods

2.1. Patient population

The study population consisted of 36 infants of gestational age (GA) from 25 to 42 weeks with clinical seizures in the first 4 weeks of life and an EEG obtained during the neonatal period (generally within 1 day of the onset of the clinical seizures) with ictal activity. We reviewed consecutive available EEGs from this patient population in which ictal events were recorded. This population over an 18-month period was retrospectively reviewed. Behavioral seizures were defined as any repetitive, stereotyped, paroxysmal activity that was felt by the physicians or nurses to lie outside the normal repertoire of behavior of newborns [13]. In this situation an EEG was typically obtained within the next 2–8 h.

Although many of the infants had serial EEGs, for purposes of this study only the first EEG recorded after the onset of the seizures was considered. Twenty-five FT infants (range 37–42 weeks GA) and 11 PT infants, defined as infants less than 37 weeks GA, were evaluated (range 25–37 weeks GA). None of the infants were paralyzed or had toxic levels of anticonvulsant at the time of the EEG. At the time of the EEG, six infants were not receiving antiepileptic drugs (three PT and three FT). The study period was for 1 year. Approximately, 65 children were suspected of having seizures during the study period. However, in 29 of these children EEG ictal events were not recorded.

2.2. EEG methods

EEGs were performed in the neurophysiology laboratory or at the bedside in the neonatal intensive care unit. A minimum of 16 channels was used and electrodes were placed using the 10–20 International System of electrode placement. Midline electrodes were used in all infants. In addition to EEG, EKG, lateral eye movements, nasal airflow and abdominal respiration were monitored. A paper speed of 30 mm/s was used routinely. Sensitivity and high- and low-frequency filter settings varied, depending on the activity recorded. Notations were made by the technologist of behavioral changes during the recording. In all instances where ictal discharges were noted a notation from the technician regarding behavioral correlates was available. The recordings continued until the infant cycled through the awake, quiet, and active sleep states. In infants without clear state changes the recording continued for a minimum of 60 min.

2.3. Assessment of EEG background activity

The EEG background activity was classified into three categories using criteria previously described by Holmes and Lombroso [14]:

1. Normal
2. Moderate abnormalities consisting of one or more of the following:
   (a) excessive discontinuity for GA
   (b) interhemispheric amplitude asymmetry
   (c) focal attenuation of amplitude
   (d) focal slowing
3. Severe abnormalities consisted of one or more of the following:
   (a) electrocerebral inactivity
   (b) low voltage invariant activity
   (c) burst suppression
   (d) permanent discontinuous activity

The presence or absence of sleep cycles were noted using criteria described by Lombroso [15] while interictal paroxysmal activity was classified as present or absent according to the criteria outlined by Holmes and Lombroso [9,14].

EEG ictal activity was arbitrarily defined as rhythmic and stereotyped activity, lasting a minimum of 10 s and having a clear beginning and end as well as an evolution in morphology and frequency [9,16,17]. All the EEG ictal discharges were classified into those with or without clinical findings.

The onset of ictal events were classified into four categories:

1. focal (when the onset was restricted to a single electrode) (Figs. 1 and 2),
2. regional (when the onset involved more than one electrode at onset) in one region (frontal, parietal, occipital, temporal) (Fig. 3),
3. unilateral (when the onset involved more than one region in the same hemisphere) (Figs. 4 and 5), and
4. bilateral (when the onset began simultaneously from both hemispheres) (Figs. 6 and 7).

Morphology at the onset and during propagation was classified into three categories using criteria described by Lombroso [15]:

(a) rhythmic discharges of beta, alpha, theta, delta range frequencies (pseudo-beta, alpha, theta, and delta) (Figs. 3, 6 and 7)
(b) low-frequency discharges (LFD) (Fig. 5)
(c) spikes, sharp waves, sharp and slow wave, spike- and wave discharges (Fig. 8)

Propagation of the discharges was classified into five

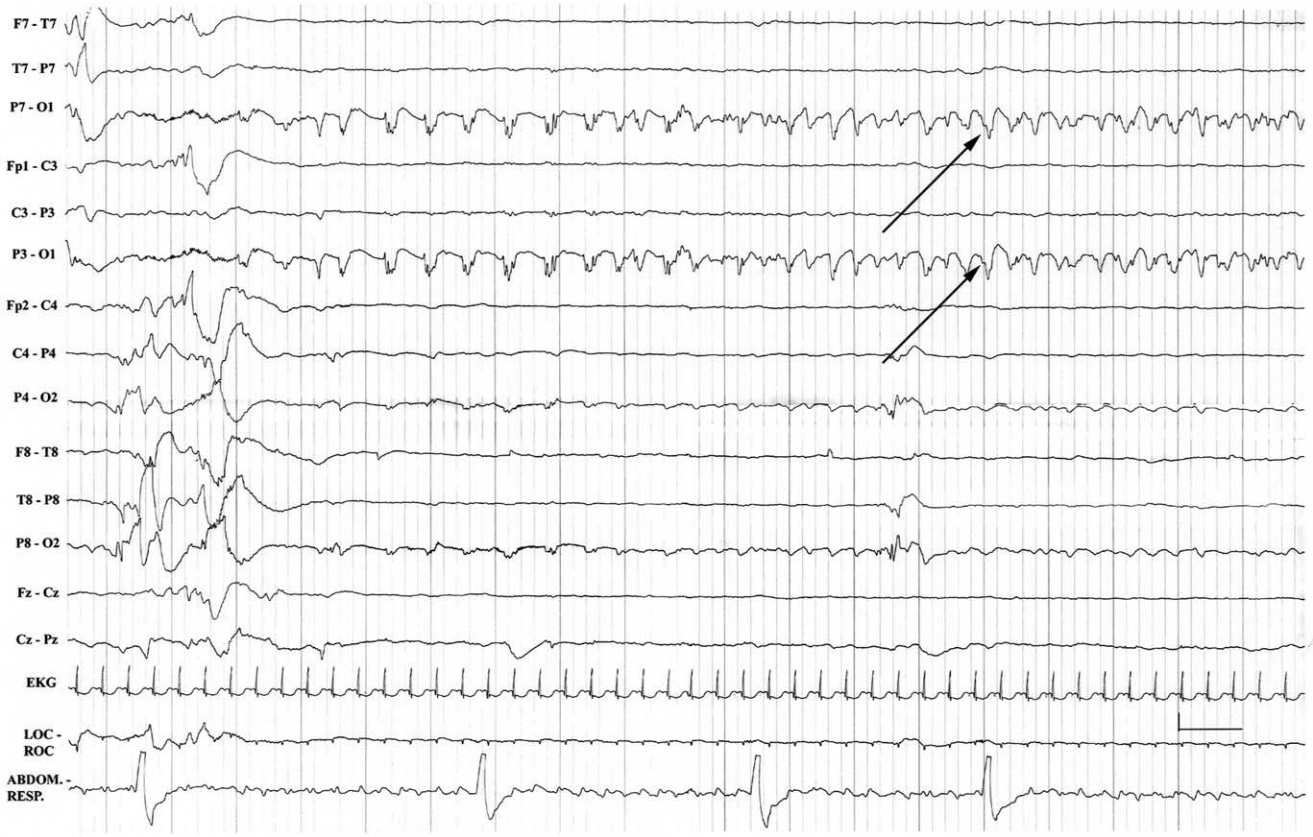

Fig. 1. Focal ictal charge beginning in the left occipital region from PT infant with hypoxic–ischemic enecephalopathy. The ictus began as a complex sharp wave and evolved into a delta discharge (arrows). EEG background was low voltage with some intermittent bursts of polymorphic delta and theta with intermixed sharp waves. Calibration 1 s and 50 μV.

categories:

1. ipsilateral
2. contralateral
3. ipsilateral at the onset and then contralateral
4. bilateral

Frequency and duration of each ictal event was also measured. Ictal disharges that changed by 2 Hz or more were characterized as having a change in frequency.

2.4. Statistics

Chi square and the Fisher's exact test were used for comparison of proportions. The Student's *t* test was used to compare group means. In all instances a $P < 0.05$ was considered significant.

3. Results

The onset of the seizures occurred in the first 3 days of life in 23 infants (63.8%), between the third and the sixth day of life in six infants (16.7%), and after the first week in seven (19.4%).

In the PT the etiologies of the seizures included intraventricular hemorrhage (IVH) in five; multifactorial causes (including IVH, cerebral dysgenesis, metabolic derangement) in three; hypoxic–ischemic encephalopathy in two, and bilateral infarctions in one. In the FT infants etiological agents included hypoxic–ischemic encephalopathy in eight, bacterial infections in three, unilateral infarction in three, cerebral dysgenesis in three, unknown causes in three, intraparenchymal hemorrhage in two, multifactorial causes in two cases, and metabolic causes in one.

The total number of EEG ictal events recorded was 156 (40 in PT and 116 in FT). The mean number of seizures per newborn was 3.64 ± 0.73 in PT (range 1–9) and 4.64 ± 0.56 in FT (range 1–12). This result was not statistically different in the two groups. The mean ictal discharge duration in the PT (97.12 ± 14.12 s, range 10–377 s) and FT (128.78 ± 14.15 s, range 10–996 s) did not differ.

Table 1 lists the background patterns recorded in the 36 patients and their relation with the number of seizures. As demonstrated in the table, only two infants, one PT and one FT, had normal background activity. Using chi square analysis, there was not a statistically significant relationship between number of seizures and background activity. Ten

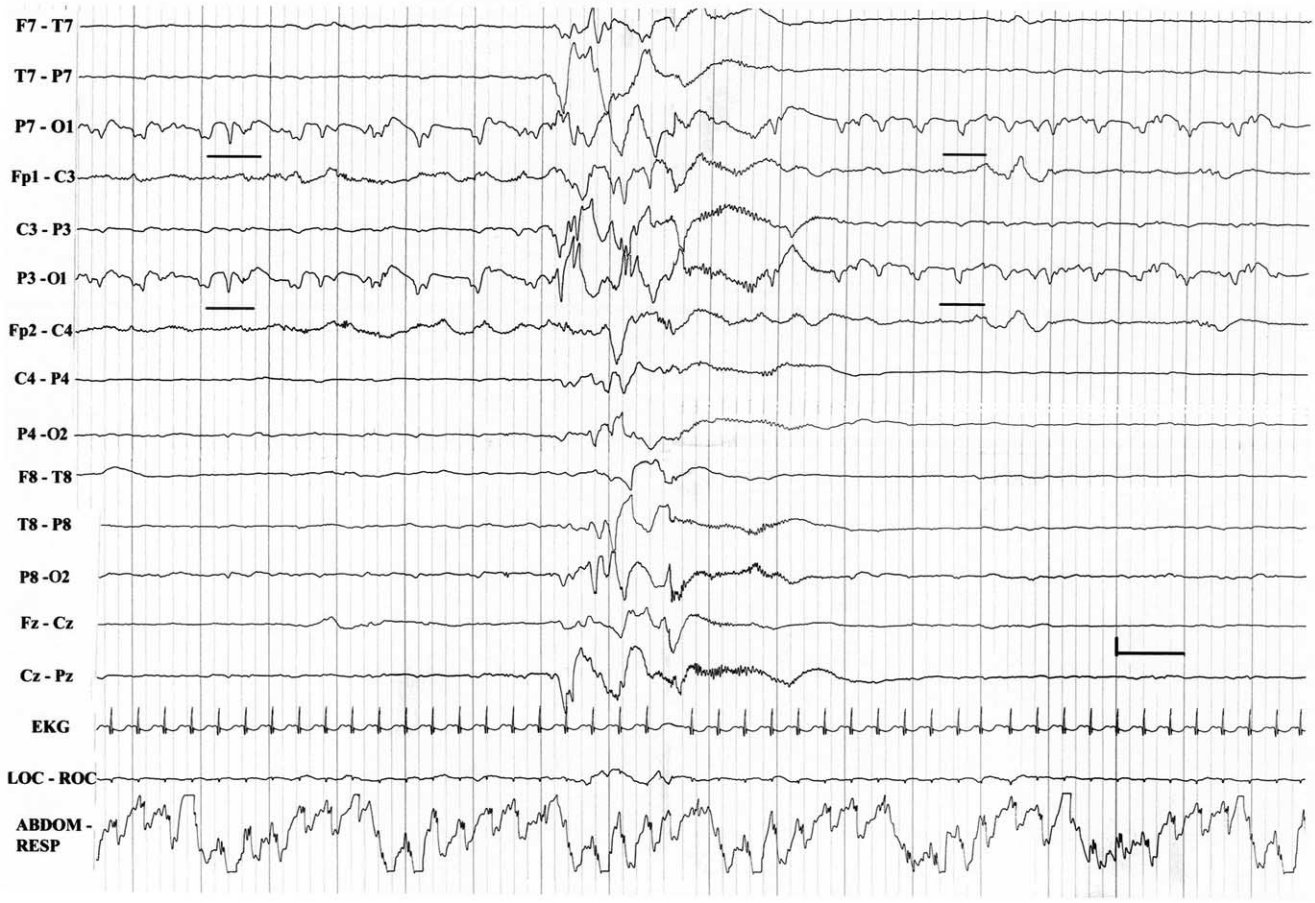

Fig. 2. Focal ictal charge beginning in the left occipital region from FT infant with hypoxic–ischemic enecephalopathy. The ictus began as a sharp wave and remained monomorphic and focal throughout the seizure. Sharp waves are underlined. EEG background was burst suppression. Calibration 1 s and 50 μV.

infants (six PT and four FT) died during the neonatal period; in all of these severe background abnormalities were found.

We compared the relationship between electrical seizures and behavioral changes as a function of background activity and presence or absence of sleep states. While electroclinical dissociation was noted more frequently in infants with severe abnormal background activity, ten of 23 (43.5.5%) with severe background abnormalities had behavioral changes associated with the EEG seizures (Table 2). There was no significant relationship between presence and absence of normal background activity and presence or absence of behavioral correlates with the ictal discharges. There was also no relationship between presence or absence and sleep state and presence or absence of behavioral changes during EEG ictal events.

Table 3 compares the location of onset of the focal ictal discharges. The temporal and central regions were the most common regions of onset. No differences in location of ictal discharges were noted in the PT and FT infants. The types of discharge at the onset and during the ictus are provided in Table 4. FT infants were more likely to have sharp waves and delta, or sharp and slow waves at the onset of the ictus while rhythmic alpha or delta was most common in the PT infants. Delta and sharp waves remained the most common

Table 1
Background abnormalities and number of seizures

	Preterm		Fullterm	
Background	#	Seizures	#	Seizures
Normal	1	1	1	2
Moderate	1	1	10	45
Severe	9	38	14	69
Total	11	40	25	116

Table 2
Background abnormalities and electroclinical relationship

	Preterm		Fullterm	
Background	E − C +	E − C −	E − C +	E − C −
Normal	1	0	1	0
Moderate	1	0	7	3
Severe	4	5	6	8

E − C +, electrical discharges associated with behavioral changes; E − C −, electrical discharges not associated with behavioral changes.

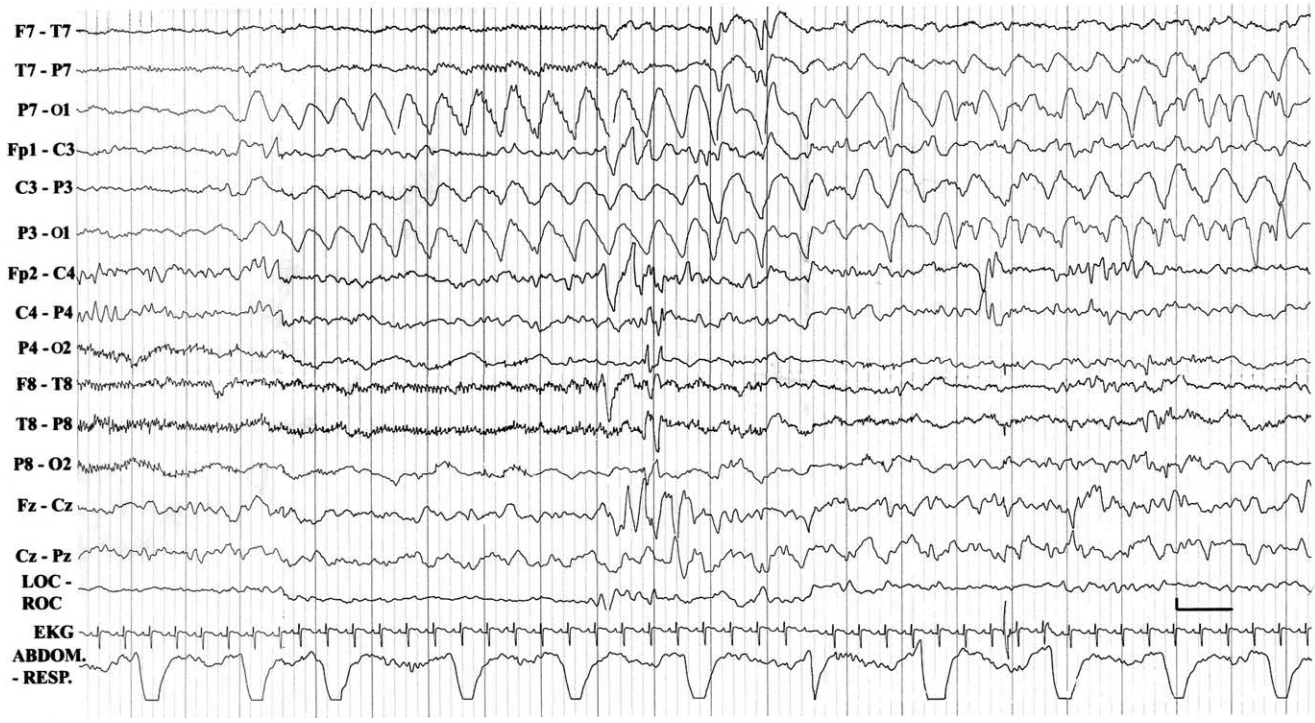

Fig. 3. Regional ictal discharge beginning in the left parietal/occipital region in PT intraventricular hemmorrhage. Note the expansion of the ictal region with time. EEG background was normal. Calibration 1 s and 50 μV.

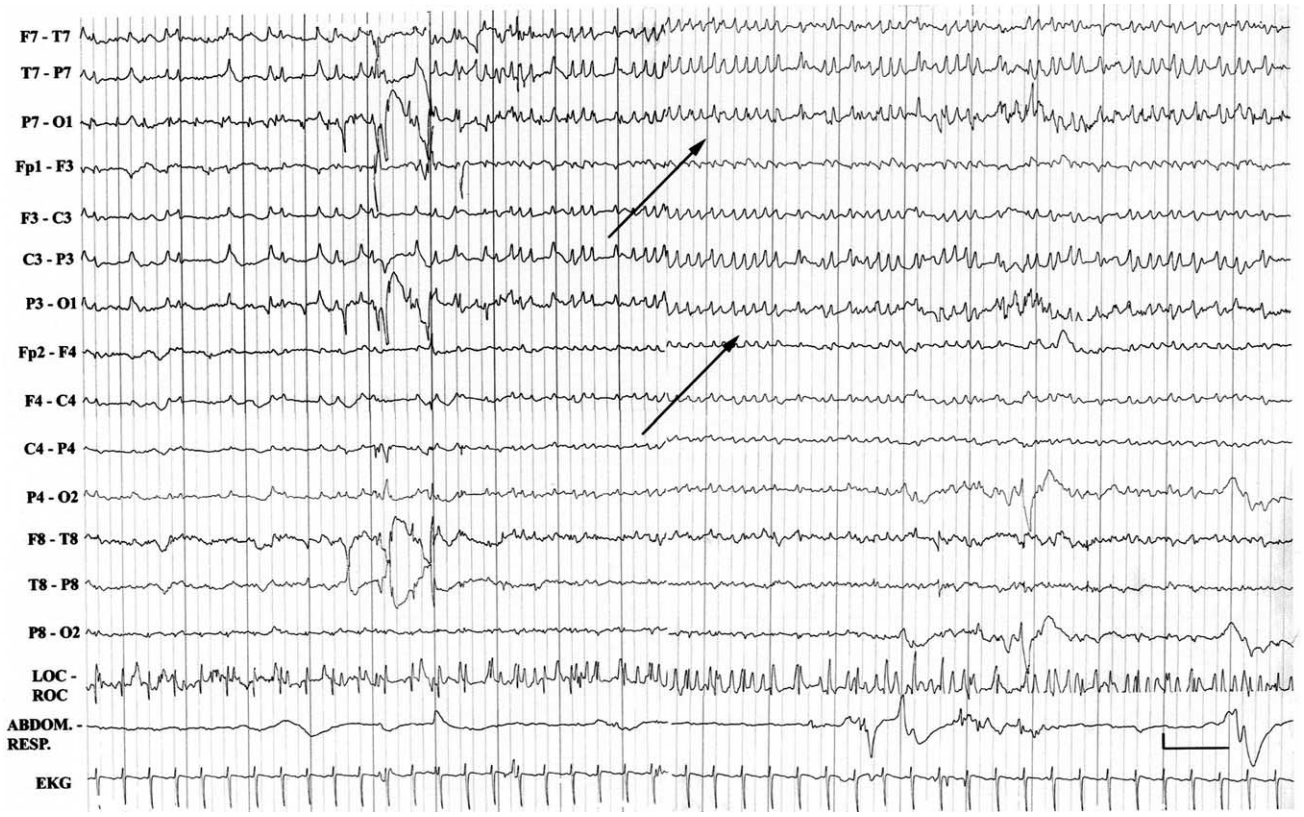

Fig. 4. Unilateral ictal discharge involving the left hemisphere in a FT infant with cortical dysplasia involving the left hemisphere. Note the change from low-frequency sharp waves to rhythmic 7 Hz sharp waves (arrows). EEG background was low voltage. Calibration 1 s and 20 μV.

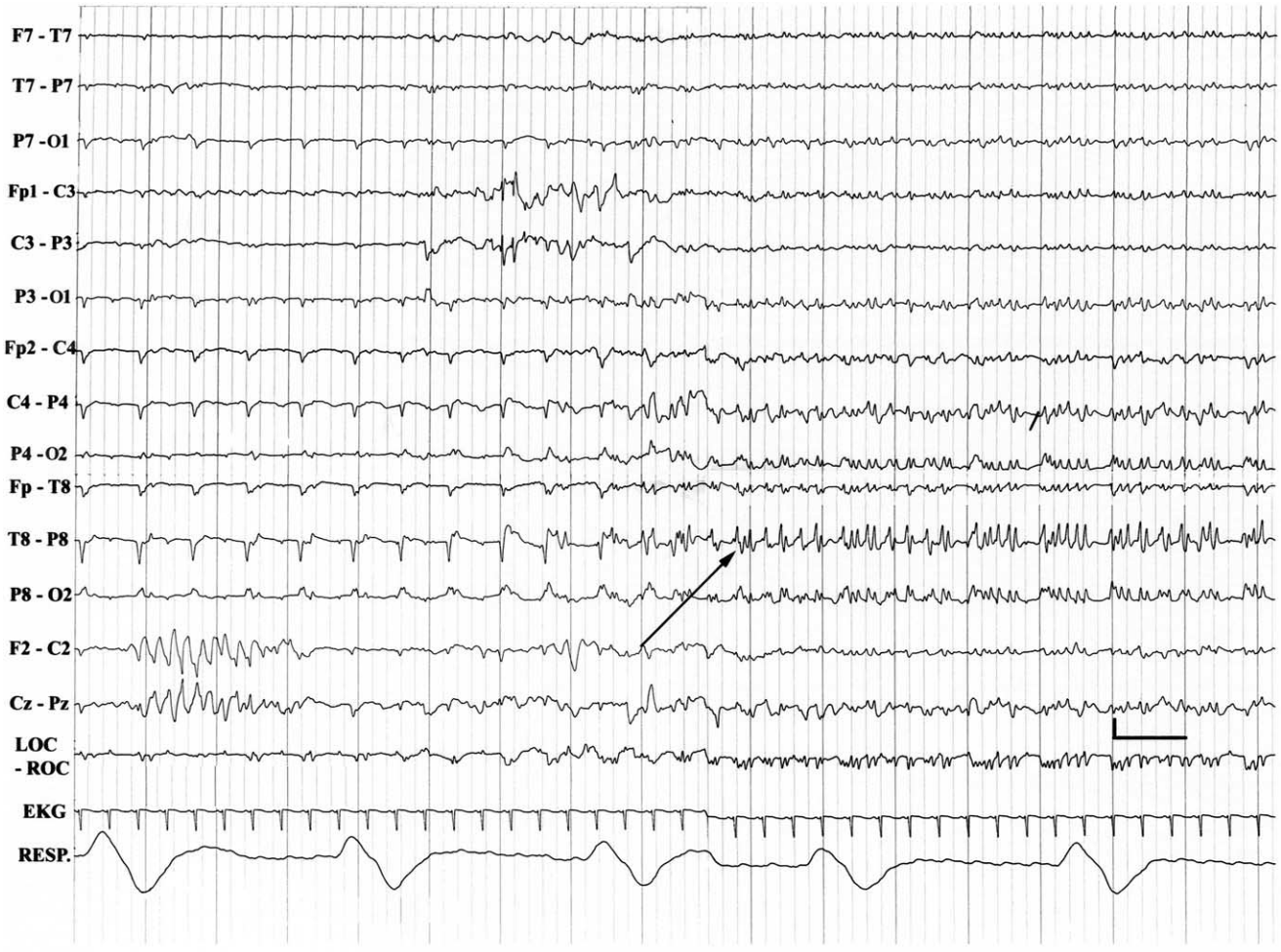

Fig. 5. Unilateral ictal discharge involving the right hemisphere in a FT infant with hypoxic–ischemic encephalopathy. Note the change in morphology and frequency of the discharges as the seizure evolves. EEG background was low voltage. Calibration 1 s and 50 μV.

ictal discharge throughout the ictus in the PT while sharp waves and delta activity were the two most common patterns in the FT infants.

Table 5 compares the type of ictal onset and changes in morphology and frequency of the ictal discharge in PT and FT infants. PT infants were most likely to start with a regional onset while the FT infants most commonly had a focal onset (Chi square = 19.86; $P < 0.001$). Bilateral onset was uncommon in both groups, but even PT infants were able to generate bilateral onset in 12.5% of the ictal discharges. Unilateral onset was present in 5.2% of FT but in none of the PT. Regardless of whether the ictal discharge began focally or regionally, a change in morphology or

Table 3
Location of onset of focal ictal discharges

Location	Preterm	Fullterm	Total	%
Frontal	3	5	8	11.3
Temporal	3	29	32	45
Central	2	17	19	26.8
Parietal	0	7	7	9.9
Occipital	0	5	5	7
Total	8	63	71	

Table 4
Type of discharge at onset and during ictus

Activity	Preterm				Fullterm			
	Onset		Dominance		Onset		Dominance	
	#	%	#	%	#	%	#	%
Beta	2	5.0	2	5.0	0	0	0	–
Alpha	9	22.5	1	2.5	1	0.9	2	1.7
Theta	1	2.5	0	–	0	0	0	–
Delta	14	35.0	18	45.0	38	32.8	38	32.8
LFD	2	5.0	0	–	13	11.2	13	11.2
Sh.	7	17.5	15	37.5	40	34.5	40	34.5
Sh. + W.	3	7.5	2	5.0	14	12.1	9	7.8
Sp.	2	5.0	2	5.0	4	3.4	8	6.9
Sp. + W.	0	0	0	–	6	5.2	6	5.2
Total	40	100	40	100	116	100	116	100

#, Number of seizures; %, percentage of seizures; LFD, low-frequency discharge; Sh., sharp waves; Sh. + W., sharp and slow wave; Sp., spikes; Sp. + W., spike and slow wave.

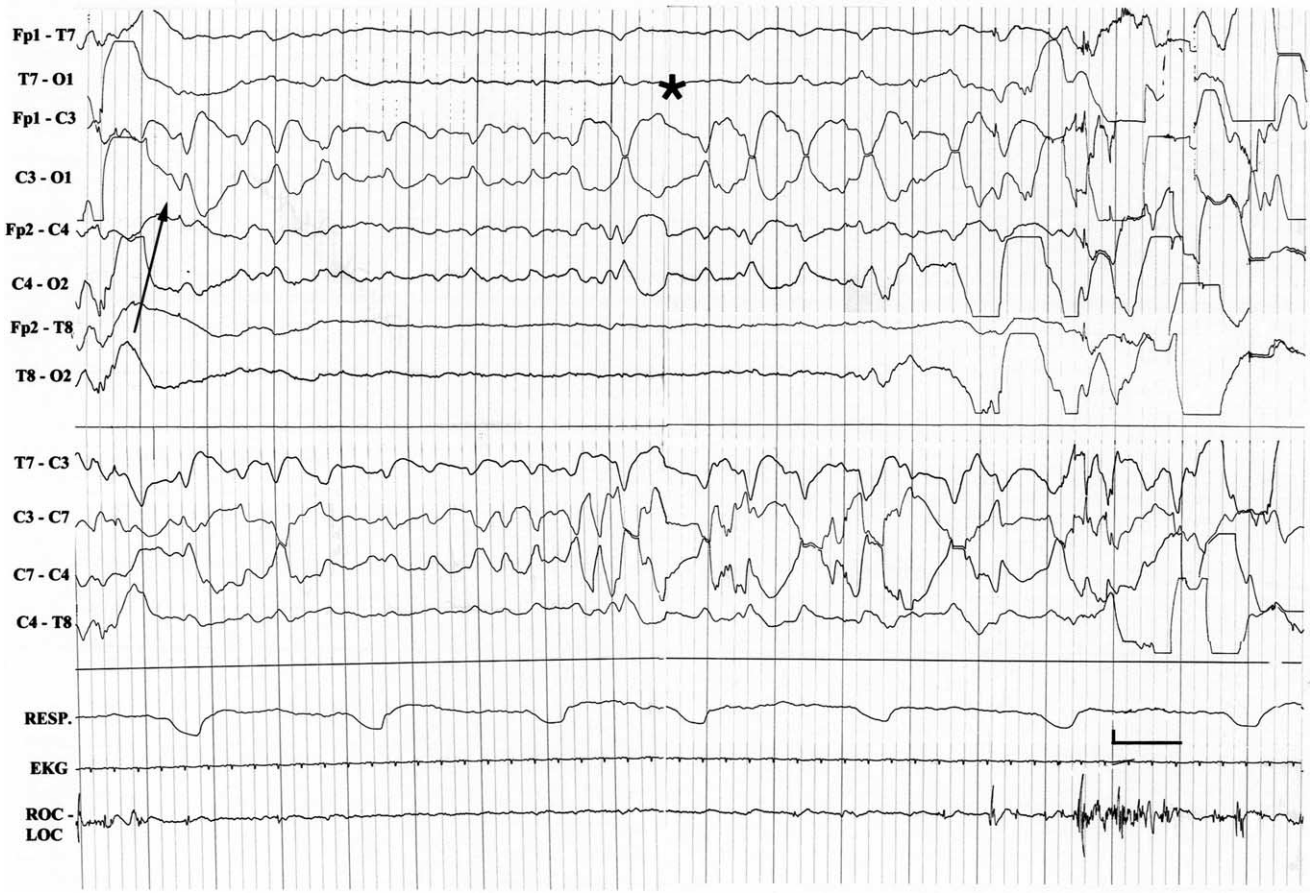

Fig. 6. Bilateral central onset to ictus in PT infant with intraventricular hemorrhage (arrow). Note the quasi-rhythmic delta which changed in morphology and frequency has the ictus continued (*). Background activity was low voltage. Calibration 1 s and 50 μV.

frequency of the discharges was common. Propagation of the ictal discharges was common. In the PT 87.5% (7/8) of the focal discharges and 77.8% (21/27) of the regional discharges propagated; in the FT 44% (28/63) of the focal discharges and 90% (36/40) of the regional discharges propagated. Propagation of the discharges was primarily ipsilateral in seizures with a focal onset, while the spread of seizures beginning regionally more frequently demonstrated a contralateral or bilateral spread in both groups (Table 6).

We compared etiology of the seizures with characteristics of the ictal discharges in both the PT and FT infants (Tables 7 and 8). The only infants with unilateral onset of the seizures were those with cerebral dysgenesis. Otherwise, there was no clear relationship between etiology and onset or morphology of the discharges.

4. Discussion

Despite the evolution of new technologies for assessing neonatal brain function, the EEG continues to be the most valuable test in the diagnosis of seizures. Sick neonates are

Table 5
Comparison of type of ictal onset and changes in morphology and frequency in PT and FT infants

	Preterm				Fullterm			
	Onset	Changes in Ictal Discharge			Onset	Changes in Ictal Discharge		
Region	# (%)	Morph.	Frequency	Both	# (%)	Morph.	Frequency	Both
Focal	8 (20)	1	0	7	63 (54.3)	26	0	2
Regional	27 (67.5)	7	0	9	40 (34.5)	17	3	9
Unilateral	0	–	–	–	6 (5.2)	3	3	3
Bilateral	5 (12.5)	0	0	0	7 (6.0)	4	0	1
Total	40	8	0	16	116	50	6	14

Morph. = morphology.

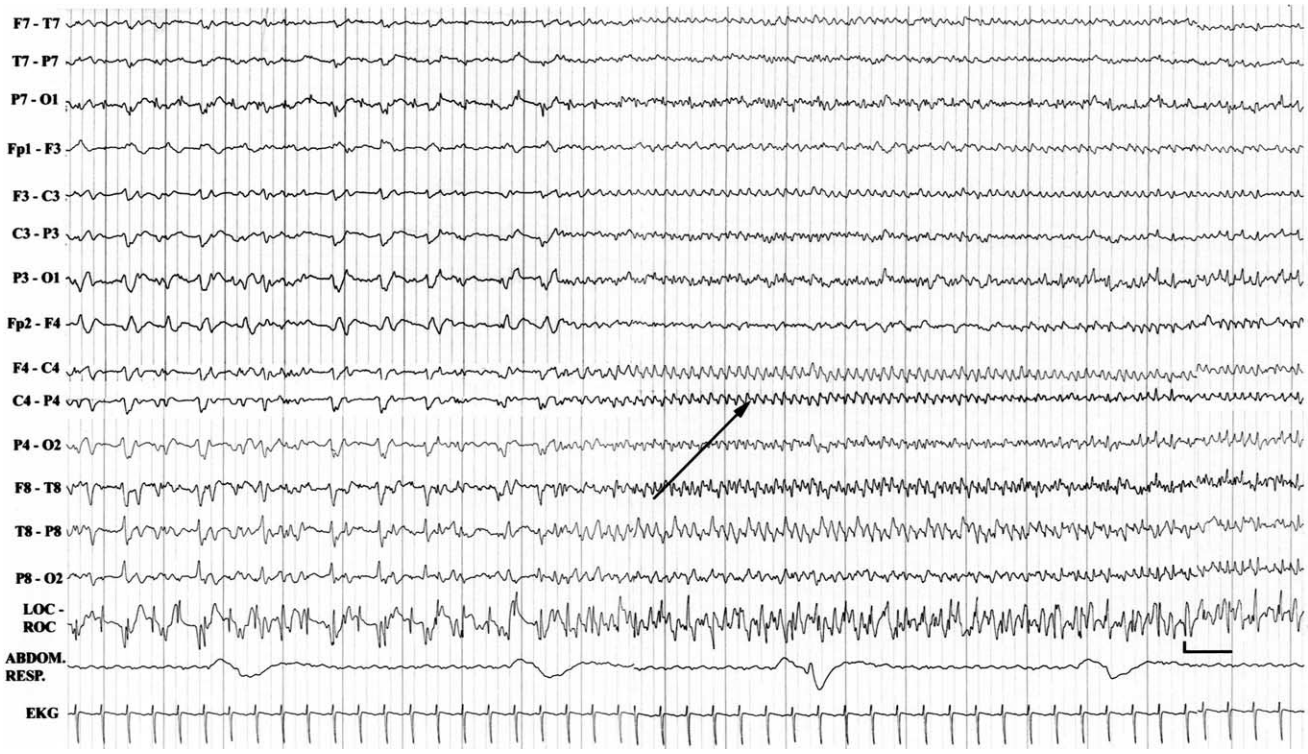

Fig. 7. Bilateral ictal onset in FT infant with multifactorial causes for his seizures. Note the change from low-frequency sharp waves to rhythmic alpha activity (R > L)(arrow). Background activity was excessively discontinuous. Calibration 1 s and 50 μV.

at high risk for subclinical seizures which can only be diagnosed with EEG [18–22]. In addition to the usefulness of EEG in diagnosing or confirming neonatal seizures, the test is a powerful prognostic tool. Infants with abnormal background activity, especially when persistent, are at risk for developmental impairment [18,23].

In this study we questioned whether the ictal pattern was related to age and etiology of the seizures. Overall, there was a considerable overlap of ictal features in the PT and FT infants. The vast majority of both PT and FT infants with electrographic seizures in this study had abnormalities of background activity. Even infants with low voltage, burst suppression, or electrical inactivity had ictal discharges, demonstrating that in the presence of severe encephalopathies the immature brain is capable of producing sustained rhythmical discharges. While the severely injured brain is readily capable of generating ictal discharges, there was a trend for those infants with severe background abnormalities and absence of sleep cycle to have an electroclinical dissociation with EEG ictal events not associated with behavioral changes. No differences between the PT and FT infants with regard to relationship of background activity and behavioral changes accompanying the EEG ictal events were seen.

The location of ictal onset was more frequently regional in PT but focal in FT. This finding was somewhat surprising in view of the reduced synaptic efficiency and myelination in the premature brain, compared to the brain at term [24]. Due to the underdevelopment of recurrent collaterals, there is poor synchrony in neocortical circuits. It is possible that a greater region of cortex may be required for ictal discharges to be detected at the surface. Additional physiological factors may be responsible for these age-related differences. It is known that the balance of excitation:inhibition favors excitation in the PT brain due to the depolarizing effects of GABA in the PT brain [25–29]. It is possible that the lack of

Table 6
Ictal discharges characteristics of propogation

	Preterm				Fullterm			
Region	Ipsilateral	Contralateral	Both	Bilateral	Ipsilateral	Contralateral	Both	Bilateral
Focal	1	0	4	2	17	4	5	2
Regional	3	5	2	11	6	5	11	14
Unilateral	0	0	0	0	0	3	0	0
Total	4	5	6	13	24	12	16	16

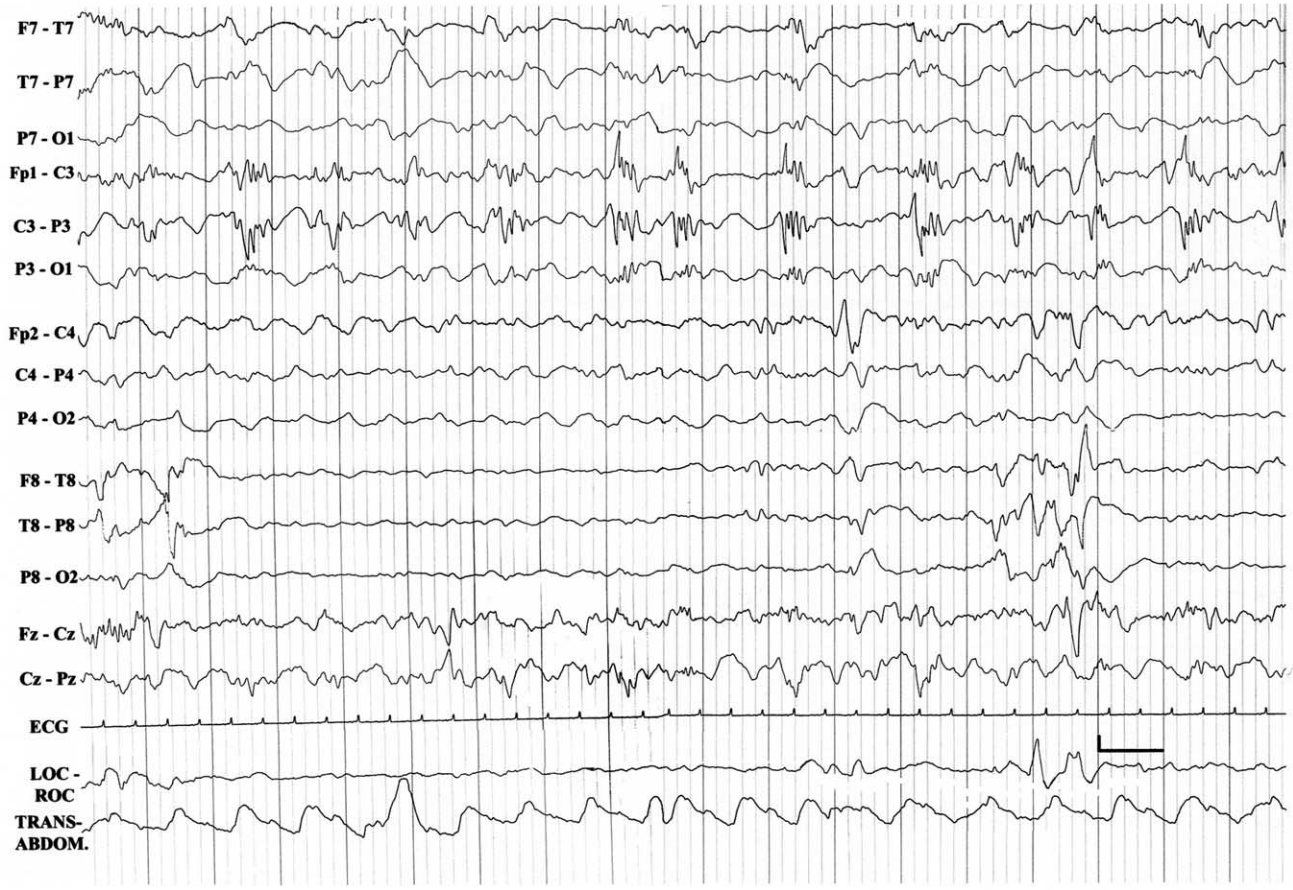

Fig. 8. Rhythmic bursts of polyspikes with a regional onset in the central region on the left. At this point in the EEG there has been some spread into the temporal and fronal region. EEG is from a PT infant with an intraventricular hemorrhage. The EEG background was excessively discontinuous. Calibration 1 s and 50 μV.

post-synaptic inhibition in the PT also results in a decreased surround inhibition resulting in a more regional seizure onset.

In both the PT and FT infants the most frequent location of focal onset was the temporal area. This propensity of the temporal lobe for seizures was not related to etiology. This ictal activity originating from the temporal area may be reflective of the particular 'epileptogenicity' of the hippocampus [30–32]. The combination of high cell density, intrinsic bursting cells, and extensive recurrent excitatory collaterals render the hippocampus highly epileptogenic [33,34].

Changes in morphology and frequency were common, involving 54% of ictal discharges. In both the PT and FT groups, these variations occurred mostly along with spatial propagation of the electrographic discharge. Seizures with a regional onset were more likely to generalize. Propagating ictal discharges were seen in 40% of PT and 25% of FT infants, demonstrating the ability of PT to generate complex ictal typology. The lack of strong inhibitory factors in the immature brain likely contributes to this propensity for spread of the discharges. The changing morphology of the discharges may be the result of a slow recruitment of additional neuronal networks during the ictus.

Table 7
Comparison of etiology and ictal characteristics in PT infants

Etiology	# of seizures (# of patients)	Onset				Morphology			Dominant Morphology		
		F	R	Lat.	Bilat.	RD	LFD	S/SW	RD	LFD	S/SW
IVH	12 (5)	16.7	83.3	–	–	75.0	–	25.0	25.0	33.3	66.7
HIE	5 (2)	40.0	20.0	–	40.0	100.0	–		100.0	–	–
Bilateral infarction	5 (1)	–	100.0	–	–	60.0	–	40.0	100.0	–	–
Multifactorial	18 (3)	22.2	61.1	–	16.7	66.7	–	33.3	44.4	–	55.5

F, focal; R, regional; Lat., lateral; RD, rhythmic discharges of delta, theta, alpha, or beta; LFD, low frequency discharges; S/SW, sharp waves, spikes,, sharp and slow wave; spike and slow wave.

Table 8
Comparison of etiology and ictal characteristics in FT infants

Etiology	# of seizures (# of patients)	Onset				Morphology			Dominant Morpho;ogy		
		F	R	Multi-focal	Bilat.	RD	LFD	S/SW	RD	LFD	S/SW
HIE	44 (8)	31.8	52.3	–	15.9	36.3	–	63.6	36.3	–	61.4
Infectious	17(3)	94.1	5.8	–	–	11.7	64.7	23.5	11.7	64.7	23.5
Unilateral infarction	11(3)	54.5	45.4	–	–	27.2	–	72.7	18.1	–	81.8
Dysgenesis	7(3)	–	57.1	42.8	–	14.2	–	85.7	28.5	–	71.4
Cerebral hemorrhage	15 (2)	73.3	26.7	–	–	53.3	–	46.7	60.0	–	40.0
Metabolic	5(1)	40.0	60.0	–	–	60.0	–	40.0	40.0	–	60.0
Multifactorial	7(2)	85.7	14.3	–	–	14.2	–	85.7	42.8	–	57.1
Unknown	10 (3)	50.0	20.0	–	30.0	60.0	10.0	30.0	60.0	10.0	30.0

F, frontal; R, regional; Lat., lateral; RD, rhtyhmic discharges of delta, theta, alpha, or beta; LFD, low frequency discharges; S/SW, sharp waves, spikes, sharp and slow wave; spike and slow wave.

One of the major aims of our study was to investigate a possible correlation between etiology of seizures and electrographic patterns of ictal activity as previously described in some neonatal encephalopathies such as herpes encephalitis [35], pyridoxine-dependent epilepsy [36], non-ketotic hyperglycinemia [37], benign familial neonatal convulsions [38], early myoclonic encephalopathy [39], and early infantile epileptic encephalopathy [40,41]. However, in this study we did not find any distinctive ictal pattern to distinguish among the more common neonatal encephalopathies. As previously described, we found that disorders causing diffuse pathology can result in focal discharges [10,15,42]. Focal seizures in the newborn do not necessarily reflect corresponding anatomical lesions. The temporal lobe, in particular, appears quite susceptible to seizures in neonates regardless of etiology.

These results of this study must be interpreted cautiously. A relatively small number of infants were studied and it is possible that with a greater number of infants we would have seen a correlation between type of ictal discharge and etiology. Another concern about the study is that despite the lack of clear electroencephalographic seizures it is possible that 'subtle' seizures were missed [7,21,43,44]. Because of the distance of the recording electrodes from the cortical surface and the limited sampling of cortical areas, particularly those occurring in midline regions, such as mesial temporal or frontal lobe structures, it is likely that some electroencephalographic seizures were not detected. In view of the increased concern about the effects of seizures on brain development it is usually prudent to defer to clinical judgement in cases where there is a clear electroclinical dissociation [45–47].

In conclusion, our results demonstrate that neonatal ictal activity is quite variable in type and location of onset, morphology, and propagation. Regardless of etiology, both term and PT infants have the ability to generate a rich variety of ictal events. While some differences occur between PT and FT infants, there is no clear relationship between any of the electrographic features of ictal events and etiology.

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