

Electroencephalographic Background and Electrographic Abnormalities in Term and Near-Term Neonates With Hyperbilirubinemia: An Observational Study

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Abstract

Background: Neonatal hyperbilirubinemia is a common condition that may progress to bilirubin-induced neurological dysfunction and permanent neurological injury. Electroencephalography (EEG) provides information regarding cerebral electrical activity, brain maturation, background organization, and electrographic seizures. Although abnormalities in sleep–wake cycling have been described in neonates with hyperbilirubinemia, less attention has been given to other EEG abnormalities, including background abnormalities and electrographic seizure activity.

Objective: To characterize EEG background abnormalities, age-related EEG maturation, and electrographic seizure or brief potentially ictal rhythmic discharge (BIRD) activity in term and near-term neonates with hyperbilirubinemia.

Methods: This observational cross-sectional study enrolled 38 term and near-term neonates with hyperbilirubinemia admitted to the neonatal intensive care unit of Cairo University Children's Hospital. Each infant underwent at least one hour of polygraphic EEG recording together with clinical and laboratory assessment. EEG background amplitude, age-appropriate graphoelements, age-dependent synchrony and continuity, and seizure/BIRD activity were assessed.

Results: Among the 38 analyzed neonates, 31 (81.6%) had normal background amplitude, while 7 (18.4%) had abnormal background amplitude. Age-appropriate graphoelements were present in 36 neonates (94.7%), while abnormalities were identified in 2 (5.3%). Age-dependent synchrony and continuity were normal in 34 neonates (89.5%) and abnormal in 4 (10.5%). Seizure activity or BIRDs were documented in 4 neonates (10.5%). One neonate had electrographic seizure activity without overt clinical seizures. The observed epileptic activity was predominantly localized to the temporal and occipital regions in the representative recordings.

Conclusion: EEG abnormalities involving background activity, age-related organization, and electrographic seizure activity were observed in a subset of term and near-term neonates with hyperbilirubinemia. These findings demonstrate that EEG may identify electrographic abnormalities that are not necessarily evident from clinical examination alone. However, because EEG was performed after treatment had already been initiated and no healthy gestational-age-matched control group was included, the findings should be interpreted as descriptive associations rather than evidence of a direct causal effect of bilirubin on EEG activity.

Keywords: neonatal hyperbilirubinemia; electroencephalography; neonatal EEG; electrographic seizures; BIRDs; bilirubin-induced neurological dysfunction; neonatal encephalopathy.

Introduction

Neonatal hyperbilirubinemia is one of the most common conditions encountered during the neonatal period. Although most cases are benign and respond to appropriate treatment, severe unconjugated hyperbilirubinemia can result in bilirubin-induced neurological dysfunction (BIND) and, in severe cases, permanent neurological injury [2,19,22,40]. Early recognition of neurological involvement is therefore an important component of neonatal care.

Electroencephalography (EEG) provides a non-invasive method of evaluating cerebral electrical activity in neonates. In addition to its established role in the detection of electrographic seizures, neonatal EEG can provide information regarding background activity, cerebral maturation, organization, synchrony, and continuity [11,12,15,18]. Abnormal neonatal EEG findings may therefore provide information about cerebral dysfunction even when overt neurological manifestations are subtle.

Previous studies have suggested that hyperbilirubinemia may influence neonatal cerebral electrical activity. Gürses and Ahiner reported effects of hyperbilirubinemia on cerebrocortical electrical activity in newborns [6]. Ter Horst et al. reported transient but delayed suppression of amplitude-integrated EEG activity in preterm infants with moderate unconjugated hyperbilirubinemia [3]. Other studies have investigated the relationship between EEG findings and bilirubin-induced neurological dysfunction, including the use of amplitude-integrated EEG as a potential predictor of neurological outcome [24,32].

Electrographic seizures are of particular clinical importance because neonatal seizures may occur without obvious clinical manifestations. Studies of neonatal seizures have emphasized the value of EEG for identifying electrographic seizure activity that may otherwise remain clinically unrecognized [5]. Zhang et al. reported temporal and occipital seizures in association with severe neonatal hyperbilirubinemia [38], raising the possibility that EEG may identify regionally specific abnormalities in affected neonates.

Despite these observations, the EEG manifestations of hyperbilirubinemia extend beyond sleep–wake cycle abnormalities. Background abnormalities, abnormal age-related graphoelements, altered continuity or synchrony, and electrographic seizure activity may provide additional information regarding cerebral function. The objective was to characterize background EEG abnormalities, age-related EEG organization, and electrographic seizure or BIRD activity in this population.

Methods

Study Design and Participants

This observational cross-sectional study enrolled 38 term and near-term neonates with hyperbilirubinemia who were admitted to the neonatal intensive care unit at Cairo University Children's Hospital.

The inclusion criteria were gestational age greater than 36 weeks and hyperbilirubinemia, defined as a total serum bilirubin (TSB) level exceeding the phototherapy threshold recommended by the American Academy of Pediatrics [8]. Neonates of either sex and all modes of delivery were eligible for inclusion provided there was no history of fetal distress.

Exclusion criteria included neurological disorders that could affect brain function, such as hypoxic-ischemic encephalopathy; comorbidities that could affect EEG findings such as congenital cardiac disease; and scalp lesions preventing appropriate EEG electrode placement.

The study was approved by the institutional research ethics committee under code MD-379-2022. Written informed consent was obtained from the legal guardians of all participating neonates.

Clinical Assessment

All neonates underwent comprehensive clinical evaluation, including detailed medical history, general physical examination, neurological assessment, laboratory investigations, and EEG recording.

The clinical history included prenatal factors, maternal medical history, maternal blood group and Rh status, family history of jaundice or hematological disorders, mode of delivery, and 5-minute APGAR score. Postnatal characteristics included gestational age, sex, birth weight, and age at onset of jaundice.

Neurological status was assessed using the bilirubin-induced neurological dysfunction (BIND) score [9]. The BIND score was assessed separately by an independent neonatologist who was not involved in EEG interpretation.

Laboratory investigations included complete blood count, hemoglobin level, reticulocyte count, serum electrolytes, serum albumin, total and fractionated bilirubin levels, blood group, and direct Coombs test [10].

All neonates received phototherapy before EEG acquisition according to institutional management protocols. Eight neonates also underwent plasma exchange in conjunction with phototherapy when clinically indicated. The duration of phototherapy before EEG recording was documented.

EEG Recording Protocol

EEG was performed in the neonatal intensive care unit using a portable Nihon Kohden (Japan) 1200-JE 921A EEG machine. Recordings were supervised by an EEG technologist and a clinical neurophysiologist.

Sleep onset, artifacts, handling, and other relevant events were documented during the recording. Electronic devices were minimized, and the incubator temperature was reduced. Each EEG recording lasted at least one hour to capture both wakefulness and sleep and was extended when artifacts interfered with interpretation [11]. The EEG settings were standardized at a 70-Hz filter, 0.3-time constant, 30 mm/s recording speed, and 10 seconds per page.

Nine scalp electrodes were used: F1, F2, Cz, C3, C4, T3, T4, O1, and O2. The electrodes were applied according to the restricted neonatal 10–20 montage described by Mizrahi and Hrachovy [12]. Additional channels for ECG, respiration, EMG, and EOG were used, yielding a 16-channel neonatal montage.

EEG Interpretation

EEG interpretation was performed according to American Clinical Neurophysiology Society terminology and neonatal EEG principles [11,12].

EEG assessment parameters:

1. Background amplitude.
2. Age-appropriate graphoelements.
3. Age-dependent synchrony and continuity.
4. Seizure and BIRD activity.

Background amplitude: normal >25 μ V, borderline 10–25 μ V [11]. Graph elements (delta brushes, frontal sharp transients, rhythmic frontal delta) were assessed; abnormalities included absent/persistent graph elements, seizures, or dysmaturity.

Age-dependent synchrony and continuity were also assessed according to the developmental characteristics expected for the infant's gestational age [11,12,15]. Electrographic seizure activity and brief potentially ictal rhythmic discharges (BIRDs) were documented when present.

Two experienced clinical neurophysiologists independently reviewed all EEG recordings. The reviewers were blinded to all clinical and laboratory information, including TSB levels, the bilirubin/albumin ratio, BIND scores, and direct Coombs test results. They were provided only with the neonate's gestational age and vigilance state because these variables are essential for accurate interpretation of neonatal EEG recordings. Any discrepancies between the two reviewers were resolved by consensus.

The principal investigator, who was responsible for patient recruitment and data management, was not blinded to the clinical information.

Statistical Analysis

Statistical analyses were conducted using SPSS version 28 (IBM Corp., Armonk, NY, USA).

Quantitative variables were presented as mean $\pm$ standard deviation, median, and range, while categorical variables were expressed as frequencies and percentages. Between-group comparisons in the original analysis were performed using the independent-samples t test or Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate.

A two-sided p value <0.05 was considered statistically significant.

Results

Study Population

Thirty-eight neonates were included, among the analyzed neonates, 22 (57.9%) were male and 16 (42.1%) were female. Thirty-one neonates (81.6%) were delivered by cesarean section, while 7 (18.4%) were delivered by normal vaginal delivery.

Maternal hypertension was present in 1 neonate's mother (2.6%), while maternal diabetes mellitus was reported in 5 cases (13.2%).

Exaggerated physiological jaundice was the most common etiology, accounting for 19 cases (50.0%), followed by ABO incompatibility in 14 cases (36.8%), Rh incompatibility in 3 cases (7.9%), and other hemolytic disorders in 2 cases (5.3%).

The direct Coombs test was positive in 11 neonates (28.9%) and negative in 27 (71.1%). According to the BIND score, 29 neonates (76.3%) had a normal score, while 9 (23.7%) had an abnormal score.

All 38 neonates (100%) received phototherapy before EEG acquisition, while 8 (21.1%) underwent additional plasma exchange.

Table 1: Demographic and clinical characteristics of the studied neonates

		Number	%
Gender	Male	22	57.9%
	Female	16	42.1%
Mode of delivery	NVD	7	18.4%
	CS (elective and emergency)	31	81.6%
Maternal History	Hypertension	1	2.6%
	Diabetes mellitus	5	13.2%

	Free	32	84.2%
Aetiology	Exaggerated physiological jaundice	19	50.0%
	ABO incompatibility	14	36.8%
	Rh incompatibility	3	7.9%
	Other hemolytic disorders	2	5.3%
Coombs test	Positive	11	28.9%
	Negative	27	71.1%
BIND score	Normal (0)	29	76.3%
	Abnormal (1-3)	9	23.7%
Treatment before EEG acquisition	Phototherapy	38	100%
	Plasma exchange + phototherapy	8	21.1%

CS: caesarean section, NVD: normal vaginal delivery

Clinical and Laboratory Characteristics

The mean gestational age was 37.61 ± 0.92 weeks, with a range of 36–40 weeks. Mean birth weight was 2.68 ± 0.51 kg. The mean 5-minute APGAR score was 8.08 ± 0.82 . The mean hemoglobin level was 14.79 ± 2.86 g/dL. The mean reticulocyte count was $7.17 \pm 6.03\%$. Mean serum albumin was 3.60 ± 0.59 g/dL, while the mean bilirubin/albumin ratio was 6.31 ± 2.21 . The mean age at onset of jaundice was 2.32 ± 1.32 days. EEG recording was performed at a mean age of 5.00 ± 1.34 days. The mean peak TSB was 22.48 ± 7.48 mg/dL. The mean TSB level at the time of EEG recording was 13.14 ± 3.47 mg/dL. The mean duration of phototherapy before EEG recording was 39.89 ± 18.34 hours.

Table 2. Clinical and laboratory characteristics of the analyzed neonates

	Mean	Standard Deviation	Median	Minimum	Maximum
Gestational Age	37.61	0.92	38.00	36.00	40.00
Birth weight	2.68	0.51	2.60	1.70	3.90
APGAR score at 5 minutes	8.08	0.82	8.00	7.00	9.00
Haemoglobin level	14.79	2.86	15.05	7.60	20.00
Age at onset of jaundice (days)	2.32	1.32	2.00	1.00	7.00
Age of patient when EEG was done	5.00	1.34	5.00	2.00	7.00
Total peak Serum bilirubin	22.48	7.48	21.00	6.60	39.00
Bilirubin level at EEG recording	13.14	3.47	13.00	6.60	23.00
Reticulocyte count	7.17	6.03	5.25	0.30	20.20
Albumin level	3.60	0.59	3.50	2.80	5.40
Bilirubin/albumin ratio (B/A) ratio	6.31	2.21	6.09	1.88	10.80
Duration of phototherapy before EEG (hours)	39.89	18.34	40.00	16.00	72.00

EEG Findings

EEG background amplitude was normal in 31 neonates (81.6%) and abnormal in 7 (18.4%).

Age-appropriate graphoelements were present in 36 neonates (94.7%), whereas abnormalities were identified in 2 neonates (5.3%). Age-dependent synchrony and continuity were normal in 34 neonates (89.5%) and abnormal in 4 (10.5%). Seizure activity or BIRDs were identified in 4 neonates (10.5%), while no seizure/BIRD activity was identified in 34 neonates (89.5%).

Table 3. EEG background analysis

Background amplitude	Normal	31	81.6%
	Abnormal	7	18.4%
Age-appropriate graphoelements	Normal	36	94.7%
	Abnormal	2	5.3%
Age dependent synchrony and continuity	Normal	34	89.5%
	Abnormal	4	10.5%
Seizure/BIRD activity	Seizures/BIRD	4	10.5%
	Normal	34	89.5%

BIRD, brief potentially ictal rhythmic discharge.

Discussion

The present study characterized non-SWC EEG abnormalities in term and near-term neonates with hyperbilirubinemia. Among the 38 analyzed neonates, abnormalities in background amplitude were identified in 18.4%, age-related graphoelement abnormalities in 5.3%, and age-dependent synchrony or continuity abnormalities in 10.5%. Electrographic seizure or BIRD activity was documented in 10.5% of the cohort.

These findings add to previous evidence that hyperbilirubinemia may be associated with alterations in neonatal cerebral electrical activity. Earlier work has described effects of hyperbilirubinemia on cerebrocortical electrical activity [6], while Ter Horst et al. reported suppression of amplitude-integrated EEG activity in preterm infants with moderate unconjugated hyperbilirubinemia [3]. Studies using amplitude-integrated EEG have also explored the relationship between abnormal cerebral electrical activity and bilirubin-induced neurological dysfunction [24,32].

Abnormal background amplitude was identified in 7 of 38 neonates (18.4%). Background activity is an important component of neonatal EEG interpretation because its characteristics vary with developmental age and can provide information about cerebral function and maturation [11,12,15].

In the present cohort, abnormalities in age-dependent synchrony and continuity were identified in 4 neonates (10.5%). These findings should be interpreted in the context of the gestational ages of the infants and the developmental characteristics of neonatal EEG. Neonatal EEG maturation is characterized by progressive changes in continuity, synchrony, and age-specific graphoelements [12,15].

Abnormal age-appropriate graphoelements were less frequent, occurring in 2 neonates (5.3%). The relatively low frequency of this finding may reflect the predominantly term and near term population of the study.

One of the clinically important findings of this study was the identification of seizure/BIRD activity in 4 neonates (10.5%). Importantly, one neonate had electrographic seizure activity without overt clinical seizures.

This observation supports the role of EEG in neonatal seizure detection. Neonatal seizures may be difficult to recognize clinically, and EEG may identify electrographic seizure activity that would otherwise remain unrecognized [5].

The temporal and occipital distribution observed in the representative recordings is also noteworthy. Zhang reported temporal and occipital seizures in association with severe neonatal hyperbilirubinemia [38]. The similarity in regional distribution provides a basis for further investigation, although the present study cannot establish that hyperbilirubinemia was the direct cause of the observed seizure activity.

The presence of electrographic abnormalities in a subset of neonates also emphasizes the importance of considering EEG evaluation when neurological dysfunction is suspected clinically. Previous work has demonstrated that EEG and amplitude-integrated EEG may provide additional information in infants at risk for bilirubin-induced neurological dysfunction [24,32].

A major consideration in interpreting the present findings is the timing of EEG acquisition.

All 38 neonates received phototherapy before EEG recording. The mean peak TSB was 22.48 ± 7.48 mg/dL, whereas the mean bilirubin level at the time of EEG recording was substantially lower at 13.14 ± 3.47 mg/dL. EEG was performed at a mean age of 5.00 ± 1.34 days, following a mean of 39.89 ± 18.34 hours of phototherapy. Consequently, the EEG recordings do not represent cerebral electrical activity at the time of peak bilirubin exposure. Treatment may have modified some electrophysiological abnormalities before EEG acquisition. Conversely, the persistence of EEG abnormalities after treatment may indicate that electrophysiological abnormalities can remain detectable despite a reduction in circulating bilirubin levels.

The lack of a direct temporal relationship between peak bilirubin and EEG recording also limits causal interpretation. Therefore, the current findings should be described as EEG abnormalities observed in neonates with hyperbilirubinemia rather than as definitive evidence that bilirubin directly produced the EEG abnormalities. The bilirubin/albumin (B/A) ratio has been investigated as a potential marker of bilirubin neurotoxicity because unbound bilirubin is considered particularly relevant to neurological exposure [35–37].

Previous studies have reported associations between bilirubin/albumin measures and neurological outcomes, although findings have varied between populations [24,35–37]. Such differences may reflect variations in bilirubin severity, population characteristics, timing of measurement, treatment status, and the neurological outcome assessed.

A positive direct Coombs test may indicate immune-mediated hemolysis and increased bilirubin production [10,33]. Similarly, the BIND score reflects clinical neurological manifestations rather than serum bilirubin concentration alone [2,22]. Future studies should specifically investigate whether these clinical markers are associated with individual EEG phenotypes, including background abnormalities and electrographic seizures.

Previous studies have demonstrated that EEG can provide information about cerebral dysfunction associated with neonatal hyperbilirubinemia. Ter Horst et al. demonstrated a transient but delayed suppression of amplitude-integrated EEG activity in preterm infants with moderate unconjugated hyperbilirubinemia [3]. The present study differs in that it involved predominantly term and near-term neonates and used conventional polygraphic EEG assessment.

Chang et al. investigated amplitude-integrated EEG in relation to acute bilirubin encephalopathy and demonstrated potential predictive utility [24]. Yuan et al. similarly evaluated early amplitude-integrated EEG in term and near-term newborns with severe hyperbilirubinemia and reported associations with long-term outcomes [32].

The current findings complement these studies by documenting conventional EEG abnormalities involving background activity and electrographic seizure/BIRD activity.

The detection of seizure activity in 10.5% of the analyzed neonates is also consistent with the broader literature emphasizing EEG monitoring in neonates at risk for seizures [5]. Zhang's report of temporal and occipital seizures in severe neonatal hyperbilirubinemia is particularly relevant to the regional distribution observed in the representative recordings from the current cohort [38].

Several aspects of the present study strengthen the interpretation of the EEG findings.

First, the EEG recordings were performed using a standardized neonatal montage with additional polygraphic channels, allowing simultaneous assessment of cerebral electrical activity and physiological signals. Second, EEG interpretation was independently performed by two experienced clinical neurophysiologists who were blinded to clinical and laboratory information, including bilirubin levels, BIND scores, B/A ratios, and direct Coombs results. This approach reduced the potential for clinical information to influence EEG interpretation. Finally, the study documented electrographic abnormalities that may not necessarily be apparent from clinical observation alone, including electrographic seizure activity without overt clinical seizures.

The findings should be interpreted in light of several limitations, including the initiation of hyperbilirubinemia treatment before EEG recording, the small single-center sample with limited representation of severe disease, the relatively short non-video EEG recordings, the absence of a healthy gestational-age-matched control group, and the lack of long-term neurodevelopmental follow-up, which collectively limit the ability to establish definitive associations and determine the prognostic significance of the observed EEG abnormalities.

Future studies should involve larger multicenter cohorts with a broader spectrum of bilirubin-related neurological dysfunction, incorporate EEG recordings before or around treatment initiation with serial and prolonged video EEG monitoring, include healthy gestational-age-matched controls and long-term neurodevelopmental follow-up.

Conclusion

In this cohort of term and near-term neonates with hyperbilirubinemia, abnormalities in EEG background amplitude, age-related organization, synchrony/continuity, and electrographic seizure/BIRD activity were observed.

Electrographic seizure or BIRD activity was identified in 10.5% of analyzed neonates, including a neonate without overt clinical seizures. Background amplitude abnormalities were identified in 18.4%, while abnormalities in age-appropriate graphoelements and age-dependent synchrony/continuity were less frequent.

These findings demonstrate that conventional EEG can identify a range of cerebral electrical abnormalities in neonates with hyperbilirubinemia, including abnormalities that may not be evident clinically. However, the timing of EEG after treatment initiation, the absence of a healthy control group, the small sample size, and the lack of longitudinal outcome data prevent conclusions regarding causality or prognostic significance.

Abbreviations

AAP: American Academy of Pediatrics

B/A: Bilirubin/albumin ratio

BIND: Bilirubin-induced neurological dysfunction

BIRD: Brief potentially ictal rhythmic discharge

CS: Cesarean section

EEG: Electroencephalography/electroencephalogram

NICU: Neonatal intensive care unit

NVD: Normal vaginal delivery

SWC: Sleep–wake cycle

TSB: Total serum bilirubin

Declarations

Ethics approval and consent to participate

The study was approved by the institutional research ethics committee under the code MD-379-2022. Informed written consent was obtained from the legal guardians of all participating neonates. Guardians were informed about the purpose of the study, the procedure, anticipated benefits, and potential risks. Participation was voluntary, and data privacy was maintained in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available because they contain information that could compromise the privacy of research participants.

Competing interests

The authors declare no competing interests.

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Authors' contributions

All authors read and approved the final manuscript.

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