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Seizures in Premature Infants Born at Less than 28 Weeks' Gestation

Irina Meledin[a, b] Hilla Tzur-Sebton[c] Iris Noyman[a, d] Michael Friger[c]
Guy Hazan[c, e] Eilon Shany[a, b]

[a]Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel; [b]Neonatal Department, Soroka University Medical Center, Beer Sheva, Israel; [c]Epidemiology Department, Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel; [d]Pediatric Neurology Unit, Soroka University Medical Center, Beer Sheva, Israel; [e]Pediatric Division, Soroka University Medical Center, Beer Sheva, Israel

Keywords
Amplitude-integrated electroencephalography · Intraventricular hemorrhage · Neonatal brain · Neonatal outcome · Mortality

Abstract
Background: The incidence of seizures in the neonatal period is thought to be high due to a lower seizure threshold of the immature brain. Data on seizures in extremely premature infants are scarce. ***Objectives:*** The aim of this study was to determine whether seizures are an independent risk factor for in-hospital death and to determine the incidence of seizures in extremely premature infants. ***Methods:*** This was a retrospective cohort study. Included were infants born under 28 weeks' gestation and monitored with amplitude-integrated electroencephalography (aEEG) over the first 3 days of life. The number and duration of seizures was retrieved from aEEG recordings together with clinical data. The association of seizures and other parameters with mortality was assessed using univariable analyses methods. Relevant parameters were used for a multivariable Cox regression analysis. ***Results:*** Overall, 229 infants were included in the study. Forty-six infants had at least one seizure episode yielding an incidence of 20%. In univariable analyses, gestational age ($p < 0.001$), birthweight Z-score ($p < 0.001$), seizures ($p = 0.025$), suppressed background aEEG ($p < 0.001$), and severe intraventricular hemorrhage (IVH; $p < 0.001$) were associated with death before discharge. In multivariable analysis, gestational age (HR = 0.61, $p < 0.001$), background aEEG activity (HR = 0.30, $p < 0.001$), birth weight Z-score (HR = 0.51, $p = 0.04$), and severe IVH (HR = 2.60, $p < 0.001$) were found to be significant predictors of mortality while the presence of seizures in the first 3 days of life trended to significantly predict an increased risk of mortality (HR = 1.53, $p = 0.09$). ***Conclusions:*** Although seizure incidence was relatively high in this cohort of extremely preterm infants and infants with seizures were more likely to die, seizures alone are not a predictor for early death. However, they may be an important indicator of pathologies that are not immediately diagnosed yet could eventually lead to death among this vulnerable population.

I.M. and H.T.-S. contributed equally to this study.
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KARGER

E-Mail karger@karger.com
www.karger.com/neo

Eilon Shany
Neonatal Department, Soroka University Medical Center
Rager Avenue 151
Beer Sheva 84101 (Israel)
E-Mail eshany@bgu.ac.il

Introduction

The incidence of seizures in the neonatal period is assumed to be higher than in any other age group [1, 2] and is associated with an increased risk of abnormal neurodevelopmental outcome [3, 4]. While in term infants hypoxic ischemic encephalopathy is the leading cause of seizures, in prematurely born infants data are scarce and the etiology is probably more varied, with intraventricular hemorrhage (IVH) occurring in the first 48 h of life as one of the possible leading causes [5].

As seizures in neonates are subtle and difficult to diagnose [6], continuous monitoring of cerebral activity is needed for their diagnosis and amplitude-integrated electroencephalography (aEEG), a method for continuous brain monitoring, is increasingly being used for that purpose. This method has been shown to be of value in the assessment of seizures in term [6, 7] and preterm infants [5].

We hypothesized that premature infants born at less than 28 weeks' gestation have a high seizure burden that is associated with poor outcome.

The primary objective of this study was to determine whether electrographic seizures during the first 3 days of life in infants born before 28 weeks' gestation are an independent risk factor for in-hospital mortality. The secondary objective was to estimate the incidence of seizures in the first 3 days of life.

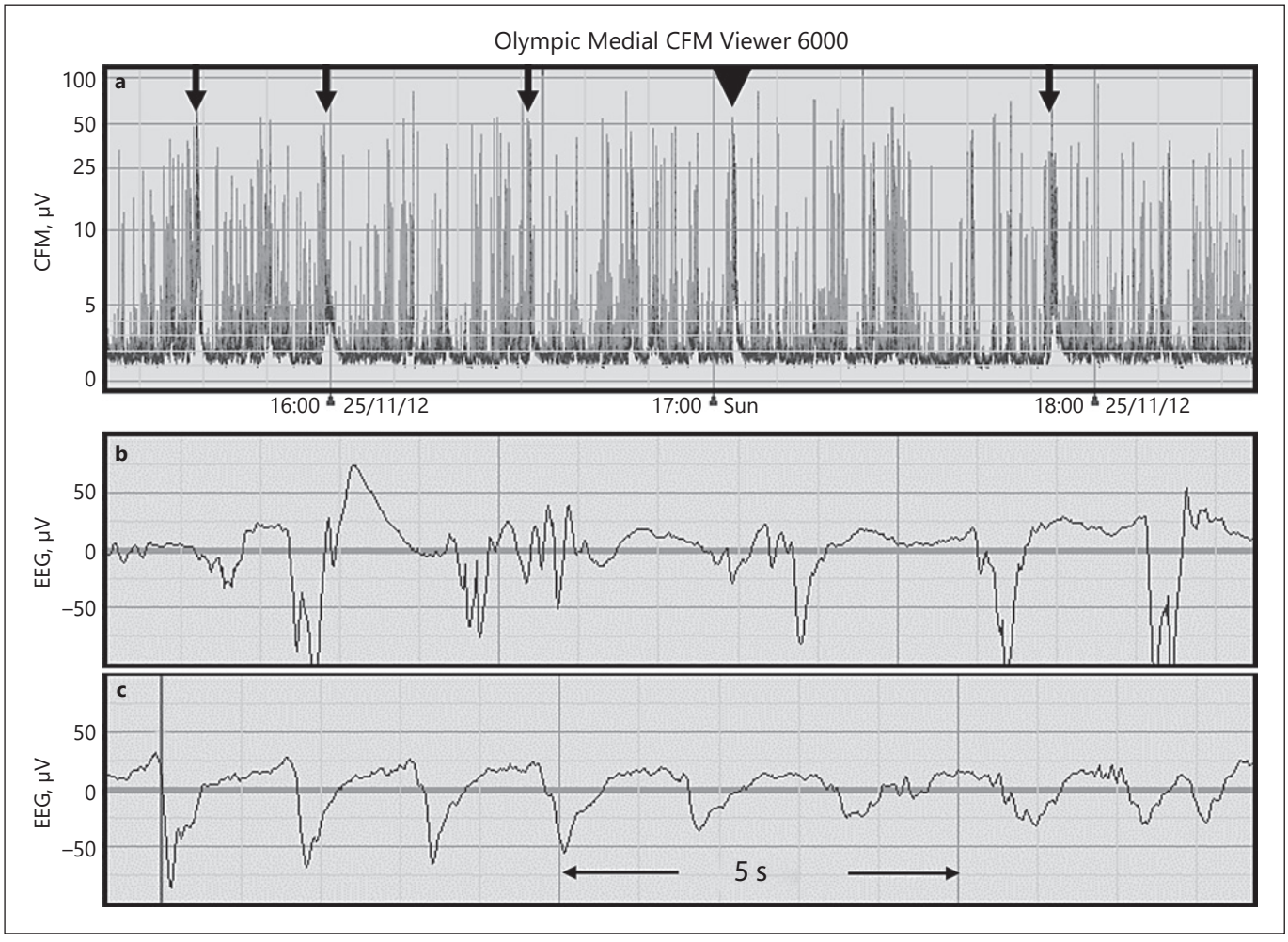


Fig. 1. An infant with IVH grade 4 and repetitive seizures in the aEEG (26 weeks' gestation at birth). **a** aEEG tracing: each arrow is positioned above a short seizure episode – a short elevation of the lower border of the aEEG tracing that was highly suggestive of seizure activity, as can be seen in **b** (the beginning of the seizure) and **c** (the end of the seizure), which are from the original EEG relating to the short period under the arrowhead in **a**. Note the decay of the rhythmic pattern suggestive of seizure activity and not artifacts. The whole seizure lasted 30 s.

Methods

This was a retrospective cohort study. Out of 443 infants born between January 2008 and June 2014 at less than 28 weeks' gestation, 229 infants monitored with aEEG in the first 3 days of life for at least 3 h were included in the study. Infants with an unreadable aEEG due to artifacts were excluded.

General demographic and clinical data were collected from the infants' files. IVH was dichotomized to grade 3 or 4 (severe IVH) versus grade 1, 2, or no hemorrhage. Use of sedation and anticonvulsants were extracted and the survival time or time to discharge was noted.

Amplitude-Integrated EEG

aEEG was recorded with the CFM 6000 recorder (Olympic Medicals, Natus, Seattle, WA, USA) that samples signals from two cup parietal electrodes. Frequencies under 2 and over 15 Hz are asymmetrically filtered after initial preamplification, then the EEG signal is rectified, smoothened, and compressed to a semilogarithmic scale. The final output reflecting the maximum and minimum amplitudes of the original EEG is displayed at a speed of 6 cm per hour [8]. As per our unit protocol, continuous aEEG monitoring is initiated in infants born at less than 28 weeks as soon as possible after delivery.

For each recording, age at the start of monitoring and the total monitoring time were noted. Seizures and their cumulative time were identified according to the criteria of Helström-Westas et al. [9] (Fig. 1). Seizure load was determined as the total cumulative time of seizures in minutes per hour of recording.

aEEG background activity was assessed and scored according to a combination of the Hellström-Westas et al. [9] and Olischar et al. [10] classifications as follows (Fig. 2): normal for age (alternation of low and high discontinuous tracing with presence of cyclicity; Fig. 2a), score = 2; suppressed (low discontinuous tracing, and burst suppression with dense bursts; Fig. 2b, c), score = 1; severely suppressed (low voltage and burst suppression with relatively sparse bursts, or isoelectric; Fig. 2d, e), score = 0. For each day, in the first 3 days of life, a daily score was ascribed according to the predominant pattern and, for the final analysis, these scores were averaged by the number of days recorded.

All recordings were assessed by 2 neonatologists (I.M., E.S.) with over 10 years of experience with aEEG seizure diagnosis and background classification. In case of disagreement, recordings were re-evaluated by the 2 researchers and if an agreement on the diagnosis of seizure pattern was not reached, a third researcher, a board-certified epileptologist, (I.N.) reviewed the tracing. Seizures were not assessed in intervals with impedance above 10 kΩ.

Statistical Analysis

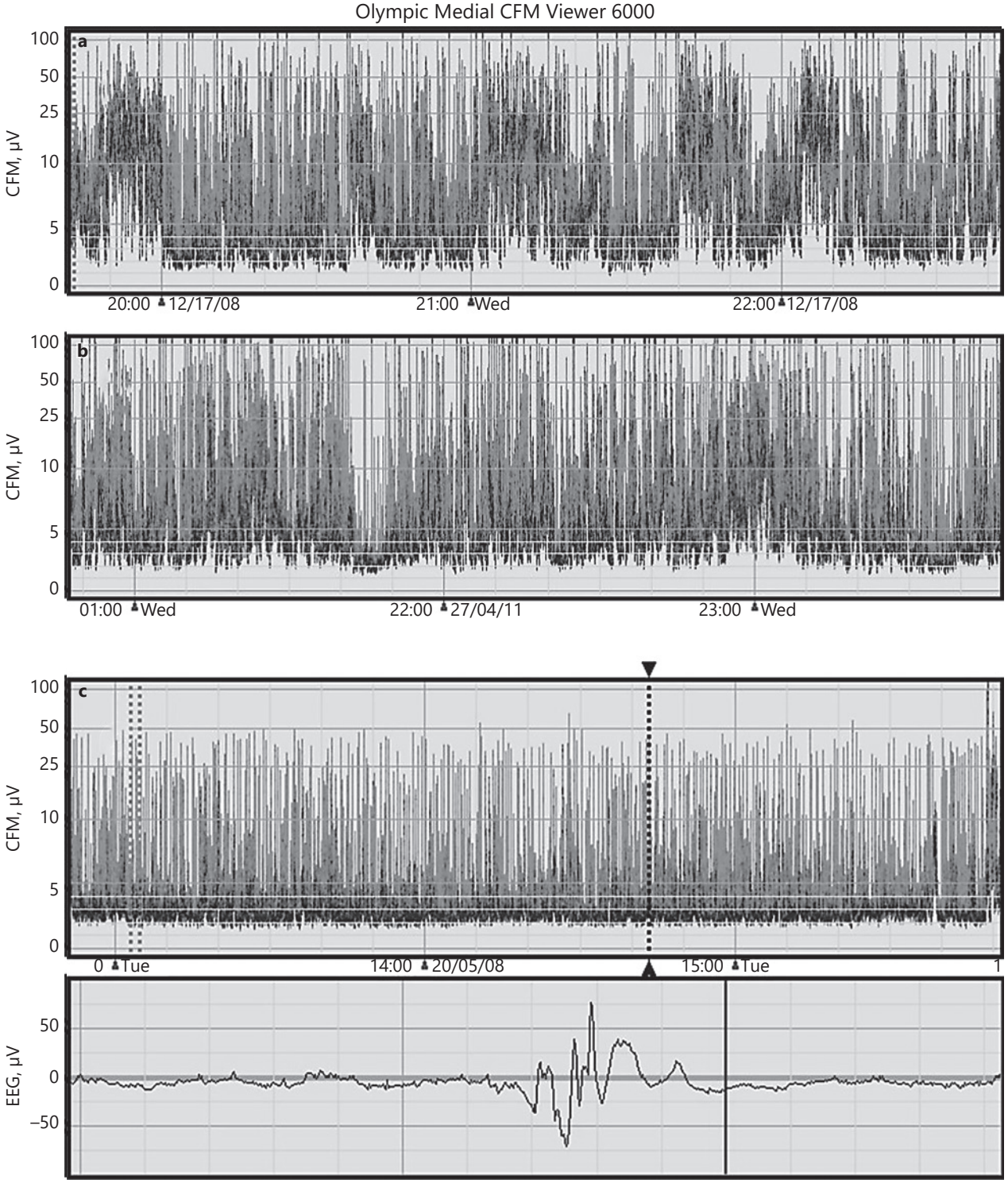
Data were analyzed with the statistical package for social sciences (IBM SPSS) version 24. Dichotomous variables were analyzed by χ^2 or Fisher exact tests as appropriate, and continuous variables were analyzed using the Student *t* test and Mann-Whitney U test as appropriate. Univariable models were repeated for validation with Cox proportional hazard analysis, and a multivariable standard backward elimination Cox model for variables associated with a *p* value <0.2 in the univariable analysis was performed. A *p* value <0.05 was considered significant. For all independent variables, confounding, multicollinearity, and interactions were ruled out.

Table 1. Clinical and demographic parameters of infants

Variable	Included in the study (*n* = 229)	Not included in the study (*n* = 119)	*p* value
GA	25.6±1.2	26.0±1.1	0.004
Alive at discharge	133 (58.1)	78 (65.5)	0.135
Weight *Z*-score	–0.0329±0.748	–0.0627±0.830	0.735
Females	107 (46.7)	56 (47.1)	0.868
Non-Jewish ethnicity	122 (53.3)	79 (66.4)	0.013
Cord pH	7.32±0.12	7.33±0.08	0.375
1-min Apgar score	5 (3–6)	5 (3–7)	0.599
5-min Apgar score	8 (6–9)	8 (7–9)	0.053
Respiratory distress syndrome	226 (98.7)	107 (89.9)	0.001
Sepsis	39 (17.0)	26 (21.8)	0.002
Necrotizing enterocolitis	28 (12.2)	13 (10.9)	0.751
Severe IVH[1]	72 (31.4)	25 (21.0)	0.041
Meningitis	8 (3.5)	1 (0.8)	0.143
Anticonvulsants	22 (9.6)	5 (4.2)	0.079
Seizures in discharge summary[2]	67 (29.3)	5 (4.2)	<0.001

Data are presented as mean ± SD, *n* (%), or median (IQR). GA, gestational age; IVH, intraventricular hemorrhage.

[1] Grade 3 and 4. [2] Seizures diagnosed at discharge summaries, including seizures after the first 3 days of life, mostly diagnosed by aEEG/EEG – therefore the numbers differ from those reported in the first 3 days of life in Table 4.



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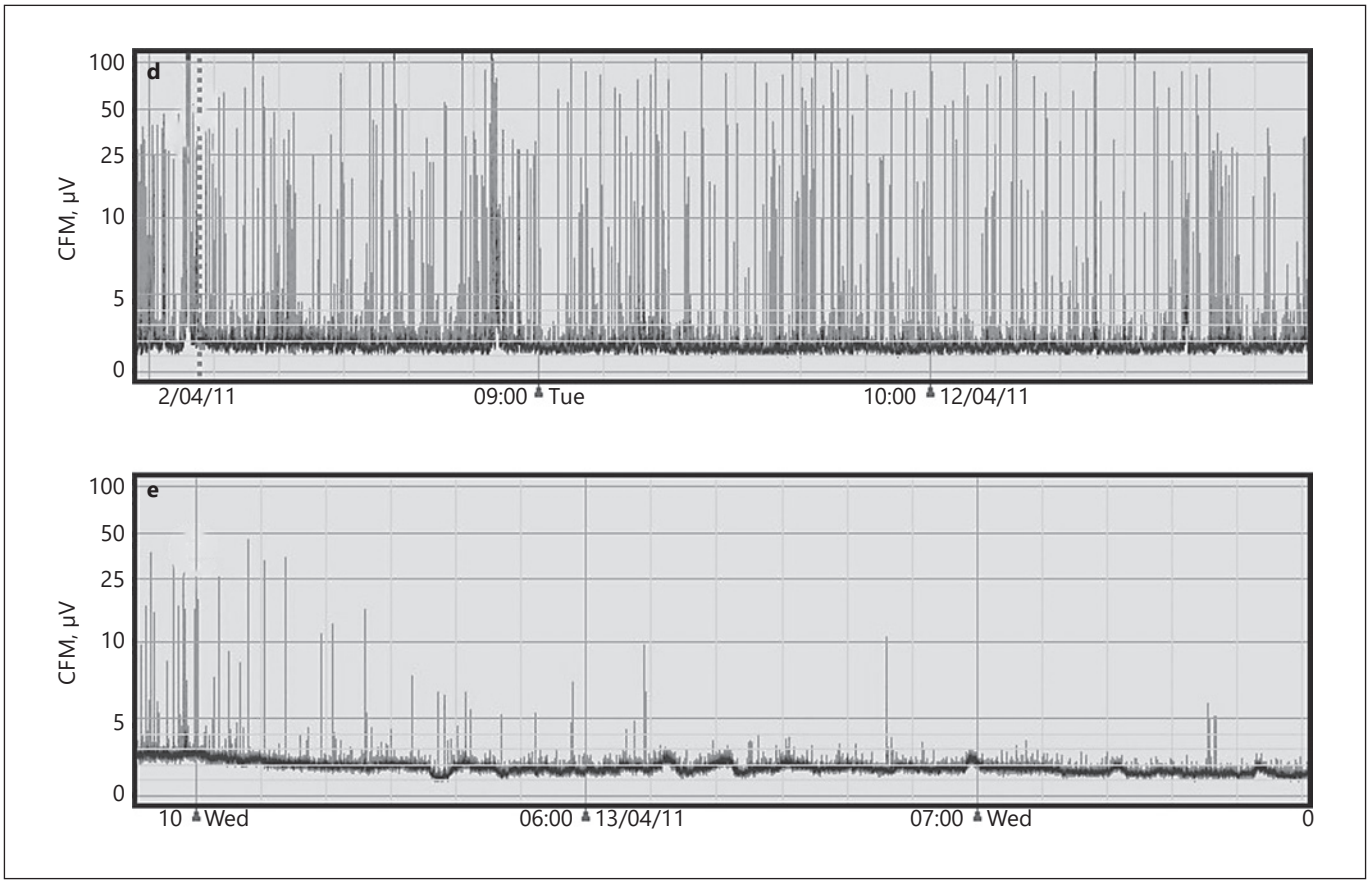

Fig. 2. Background pattern classification and scoring. **a** The aEEG band alternates between low and high discontinuous creating cyclicity (score 2). **b** Low discontinuous tracing. Note the lower border of the aEEG that is fluctuating slightly but generally suppressed (score 1). **c** Burst suppression with dense bursts. Note that the lower border of the aEEG is continuously low, below 3 µV. The lower panel of this figure depicts the original EEG relating to the arrowhead period in the panel above. Note the nearly isoelectric background with a burst of electrical activity towards the second half of the tracing (score 1). **d** Burst suppression with relatively sparse bursts (score 0). **e** Isoelectric tracing (score 0).

Results

During the study period 443 infants were born at less than 28 weeks' gestation; 95 died in the delivery room due to extreme prematurity or lethal congenital malformations and 119 were not included due to technical problems (n = 24), monitoring that started after 3 days of life (n = 16), and unavailability of a monitor (n = 79). The inclusion criteria were met by 229 infants.

Clinical and demographic parameters of the infants in the cohort and their comparison with infants not included in the study but surviving the delivery room are presented in Table 1. Infants who were not included in the study were slightly more mature (26 vs. 25.6 weeks gestational age [GA] at birth, p = 0.004), were more likely to be of non-Jewish ethnicity (66.9 vs. 53%, p = 0.013), and were less likely to be diagnosed with respiratory distress syndrome (90.7 vs. 98.3%, p = 0.001), sepsis (22 vs. 38.7%, p = 0.002), severe IVH (21.2 vs. 31.6%, p = 0.041), or seizures at discharge (4.2 vs. 19.3%, p < 0.001).

Of the 229 preterm newborns suitable for analysis, slightly more than half were males (54.7%) and 133 (58%) survived to discharge. Comparisons between infants who survived and those who did not survive are presented in Table 2. Survivors tended to have higher GA at birth (26 vs. 25 weeks, p < 0.001), higher birth weight Z-scores (0.159 vs. –0.294, p < 0.001), and higher 1-min Apgar scores (5 vs. 4, p = 0.04). Nonsurvivors tended to have a higher incidence of severe IVH (57 vs. 14%, p < 0.001), and were more likely to be treated with phenobarbital (10 vs. 1.5%, p = 0.005) and with morphine (84 vs. 55%, p < 0.001). Infants with seizures were more likely to also be

Table 2. Basic demographic and clinical characteristics compared by survival to discharge

Variable	Dead (n = 96)	Alive (n = 133)	p value
Term	25.02±1.09	26.04±1.01	<0.001
Male sex	49 (51.0)	74 (55.6)	0.49
Non-Jewish ethnicity	49 (51.0)	73 (54.9)	0.57
Cesarean delivery	54 (56.3)	78 (58.6)	0.72
Birth weight Z-score	–0.294±0.8	0.159±0.64	<0.001
Head circumference Z-score	–0.140±1.34	0.150±1.12	0.078
Cord pH	7.33±0.11	7.31±0.14	0.316
1-min Apgar score	4 (3–6)	5 (3.25–7)	0.04
5-min Apgar score	8 (6–9)	8 (7–9)	0.121
Severe IVH[1]	53 (56.4)	18 (13.5)	<0.001
Respiratory distress syndrome	94 (97.9)	131 (98.5)	1
Sepsis	35 (36.5)	54 (40.6)	0.53
Necrotizing enterocolitis	16 (16.7)	12 (9)	0.08
Meningitis	3 (3.1)	5 (3.8)	1
Phenobarbital	10 (10.4)	2 (1.5)	0.005
Total hours monitored[2]	55 (49–68)	60 (56–69)	0.49
Hospitalization days[3]	6 (3–15.75)	80 (68–96.5)	<0.001

Data are presented as mean ± SD, n (%), or median (IQR). Univariable analysis: Student t test, χ^2 and Mann-Whitney U test, as appropriate. IVH, intraventricular hemorrhage.

[1] Grade 3 and 4. [2] In the first 72 h of life. [3] This item represents the median (IQR) time to death in the non-survivors, which was much shorter than the length of hospitalization in survivors.

Table 3. aEEG characteristics compared by survival to discharge

Variable			Dead	Alive	p value
Day 1	Available recordings for analysis		n = 93	n = 118	
	aEEG seizures		10 (10.8)	10 (7.8)	0.452
	background activity:	severely depressed	15 (16.1)	5 (3.9)	<0.001
		moderately depressed	60 (64.5)	59 (46.1)	
		normal	18 (19.4)	64 (50)	
Day 2	Available recordings for analysis		n = 83	n = 126	
	aEEG seizures		14 (16.9)	7 (5.6)	0.008
	background activity:	severely depressed	19 (22.9)	4 (3.2)	<0.001
		moderately depressed	44 (53)	44 (34.9)	
		normal	20 (24.1)	78 (61.9)	
Day 3	Available recordings for analysis		n = 79	n = 120	
	aEEG seizures		12 (15.2)	10 (8.3)	0.131
	background activity:	severely depressed	18 (22.8)	2 (1.7)	<0.001
		moderately depressed	39 (49.4)	30 (25.0)	
		normal	22 (27.8)	87 (73.3)	
First 3 days	Available recordings for analysis		n = 96	n = 133	
	aEEG seizures		26 (27.1)	20 (15)	0.025
	Seizure load[1]		0.27 (0.005–10.24)	0.24 (0.05-4.57)	0.8
	Mean background activity score[2]		1 (0.67–1.33)	1.67 (1.33–2)	<0.001

Data are presented as n (%) or median (IQR). Univariable analysis: χ^2 and Mann-Whitney U test, as appropriate. n varies within days as the number of available aEEG recordings vary due to either a delay in initiation of the recording or death on the first or second day of life.

[1] Computed as total seizing time (in minutes) divided by total monitoring time (in hours); comparison was made only within infants with seizures. [2] Computed as the average activity in the first 3 days, where 0 is severely depressed, 1 is moderately depressed, and 2 is normal.

diagnosed with severe IVH (59 vs. 24%, $p < 0.001$) and had a shorter hospitalization stay (35.5 days vs. 67, $p = 0.003$), probably related to their higher mortality rate.

Comparisons of aEEG characteristics between the two groups are presented in Table 3. Significant differences in background activity were found in all 3 days of aEEG monitoring between the two groups. Thus, for example, on the first day of life in the group of infants who died, 16.1% had a severely suppressed background activity and 19.4% had normal activity, as compared to 3.9% with severely suppressed activity and 50% with normal activity in the group who survived ($p < 0.001$). aEEG seizures were diagnosed in 46 (20%) infants during the first 3 days of life (27.1% of the group who died compared to 15% of the group who survived, $p = 0.025$).

In the multivariable analysis (Table 4), GA ($p < 0.001$), birthweight *Z*-score ($p = 0.04$), severe IVH ($p < 0.001$), and suppressed aEEG background activity ($p < 0.001$) were found to be significant predictors of mortality, while the presence of seizures in the first 3 days of life only trended to significantly predict an increased risk of mortality (HR = 1.53, 95% CI 0.94–1.49). Treatment with morphine was not found to be an independent predictor.

Forty-six infants had at least one seizure episode during the first 3 days of life, yielding a seizure incidence of 20%. Assuming that none of the 118 infants who survived in the delivery room and were not monitored had any seizure during the first 3 days of life, a more realistic estimation of seizure incidence at our center during the study period would be 13.2%.

Table 4. Multivariable Cox proportional hazards regression model for the prediction of mortality with interaction variables

Variable	HR (95% CI)	*p* value
Any seizure in first 3 days of life	1.53 (0.94–2.49)	0.09
Background activity	0.30 (0.2–0.44)	<0.001
GA	0.61 (0.5–0.74)	<0.001
Birthweight *Z*-score	0.51 (0.39–0.67)	<0.001
Severe IVH	2.60 (1.63–4.14)	<0.001

CI, Confidence interval, HR, hazard ratio; GA, gestational age; IVH, intraventricular hemorrhage.

Discussion

In this cohort of 229 premature infants born before 28 weeks, we found that the incidence of seizures during the first 3 days of life ranged between 20 and 13%. Infants who had aEEG-confirmed seizures were more likely to die before discharge from the hospital compared to those who did not have any seizures. However, in the multivariable analysis, GA, background aEEG activity, birthweight *Z*-score, and grade 3/4 IVH were found to be stronger predictors of mortality.

Several authors have explored neonatal seizures in prematurely born infants using different methodologies. The group of Pisani et al. [3, 11, 12] explored several aspects of neonatal seizures. In their first study [3] a cohort of 51 (6%) out of 835 premature infants with clinically suspected, EEG-confirmed seizures was assessed. The aim was to identify early risk factors predicting adverse outcome within the infant group with seizures. Infants surviving to hospital discharge had high rates of death and adverse neurodevelopmental outcome, which were mainly related to 1-min Apgar score and to severe EEG background activity irrespective of GA at birth. The aim of the second study [11], based on a cohort of 403 infants, was to assess if seizures in infants born at less than 32 weeks GA were predictive of in-hospital death. The incidence of seizures in this cohort was 8.6% ($n = 35$), but, similarly to our study, although infants with seizures were more likely to die (37.1% mortality compared to 16.5%), only severe IVH in a subgroup of infants born under 1,000 g was found to be an independent risk factor predicting mortality. Lastly, in 2016, in a subgroup of 76 high-risk premature infants with EEG-confirmed seizures, Pisani et al. [12] found a sensitivity of 85% for the prediction of adverse outcome in a multivariable model that included birth weight, 1-min Apgar score, neurological examination, background EEG, status epilepticus, and cerebral ultrasound.

Three studies reported on aEEG monitoring in the first days of life in infants under 30 weeks GA. Shah et al. [5] found a seizure incidence of 22% in 51 consecutively enrolled infants. As in our study, seizures were associated with death and with IVH. In the second, Wikström et al. [13] reported on the aEEG of 49 prospectively recruited infants. In 21 (43%) recordings, seizure activity was diagnosed. Seizures were more prevalent, in this cohort, in infants with brain injury (any IVH or periventricular leukomalacia) but were not correlated to outcome. Despite the low percentage of severe IVH (16%) reported in their study, the prevalence of seizures was much higher than in our cohort, and this might be due to a selection bias as infants were not consecutively enrolled. In a larger study that included 95 very preterm infants, Vesoulis et al. [14] found a seizure incidence of 48% in the first 3 days of life.

Again, seizures were associated with IVH and white matter injury, but also with outcome (death before discharge and poorer language development). These cohorts, though, were too small for a multivariable analysis. Lastly, a recent study by Lloyd et al. [15] reported on a cohort of 120 infants under 32 weeks GA who had a continuous multichannel EEG recorded during the first 3 days of life. In this cohort, only 6 (5%) infants were diagnosed with seizures. Although a much lower incidence than in our study and those of others, it should be noted that the overall mortality in this cohort was low (6.6%) as was the incidence of severe IVH (9%), but as in our study, infants with seizures were more likely to have severe IVH (6 vs. 50%) and to die (5 vs. 33%). Although the incidence of seizures in different reports is variable and depends on the diagnostic method and degree of prematurity, in most studies the outcome depends on related comorbidities (mainly IVH). Moreover, as highlighted in Davis et al. [16], infants with seizures surviving the neonatal period are at significant risk for adverse outcome.

In a recent study by Weeke et al. [17] the authors tried to classify different rhythmic patterns detected in a two-channel aEEG recorder in the first 72 h of life and relate them to outcome in a cohort of 77 infants born at less than 28 weeks GA. Although rhythmic discharges were detected in 63.3% of the cohort, the authors reported that ictal discharges were clearly demonstrated in only 1 infant with severe brain injury. Other types of rhythmic patterns, such as periodic epileptiform discharges, zeta waves, and sinusoidal patterns, described in older children and adults were related by the authors to head position but not to outcome, and therefore were considered artifacts. In 44% of the cases, periodic epileptiform discharges were detected and their duration but not incidence had a borderline association with brain injury. This study underscores the importance of clearly defining seizure activity and differentiating it from artifacts in the electromagnetic noisy intensive care environment. Many of the rhythmic activities detected in the brain monitors (especially those equipped with seizure-detection algorithms) should be carefully examined for evolution in amplitude, pattern, and frequency, and even when seizures are diagnosed in the extremely premature infant caution should be exerted before antiepileptic treatment is initiated. This cohort is not comparable to ours as the incidence of brain injury was much lower than ours (11.7%) and the recordings were acquired from two lateral channels. Also, we believe that most of the rhythmic discharges considered as artifacts in the study by Weeke at al. [17] were discarded as such in our cohort, since a key condition in our inclusion criteria for diagnosing seizures included the evolution of the discharges.

The main strengths of our study are that seizures were diagnosed electrographically and the relatively large cohort, which enabled a multivariable analysis. The main limitations of this study are its retrospective nature and lack of long-term neurodevelopmental outcomes. As shown in Table 1, this caused an inclusion bias towards a cohort of lower GA and sicker infants. Considering that the main predictors of mortality were less likely to occur in the infants that were not recorded (severe IVH and suppressed background activity), we suppose that their inclusion might not have changed our results. Also, due to the retrospective nature of the study, some parameters, such as obstetrics, prenatal steroids therapy, time on ventilator, and parental wish to withdraw treatment, could not be collected and included in the analysis. Another important limitation is that it was a single-center study and the incidence of seizures in our cohort relates to the prevalent morbidities and mortality in our unit. The use of aEEG is another limitation in this study, but multichannel EEG is not applicable in the routine care of very premature infants, and aEEG with access to the original EEG is a reliable tool in the hands of experienced clinicians [6].

Conclusions

The incidence of seizures in premature infants born at less than 28 weeks during the first 3 days of life ranges between 13 and 20%. While seizures were not found to be an independent risk factor for death before discharge, they could be an important indicator of cerebral pathology, mainly severe IVH, which is not always immediately diagnosed, yet is independently correlated to mortality. Our study also highlights a high incidence of unrecognized and untreated seizures in this age group.

Statement of Ethics

The study protocol was approved by the Soroka Medical Center ethics committee.

Disclosure Statement

The authors have no conflicts of interest to declare.

References

1 Hauser WA, Annegers JF, Rocca WA. Descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester, Minnesota. Mayo Clin Proc. 1996 Jun;71(6):576–86.

2 Levene M. The clinical conundrum of neonatal seizures. Arch Dis Child Fetal Neonatal Ed. 2002 Mar;86(2):F75–7.

3 Pisani F, Barilli AL, Sisti L, Bevilacqua G, Seri S. Preterm infants with video-EEG confirmed seizures: outcome at 30 months of age. Brain Dev. 2008 Jan;30(1):20–30.

4 Khan RL, Nunes ML, Garcias da Silva LF, da Costa JC. Predictive value of sequential electroencephalogram (EEG) in neonates with seizures and its relation to neurological outcome. J Child Neurol. 2008 Feb;23(2):144–50.

5 Shah DK, Zempel J, Barton T, Lukas K, Inder TE. Electrographic seizures in preterm infants during the first week of life are associated with cerebral injury. Pediatr Res. 2010 Jan;67(1):102–6.

6 Frenkel N, Friger M, Meledin I, Berger I, Marks K, Bassan H, et al. Neonatal seizure recognition—comparative study of continuous-amplitude integrated EEG versus short conventional EEG recordings. Clin Neurophysiol. 2011 Jun;122(6):1091–7.

7 Bourez-Swart MD, van Rooij L, Rizzo C, de Vries LS, Toet MC, Gebbink TA, et al. Detection of subclinical electroencephalographic seizure patterns with multichannel amplitude-integrated EEG in full-term neonates. Clin Neurophysiol. 2009 Nov;120(11):1916–22.

8 Prior PF, Maynard DE, Sheaff PC, Simpson BR, Strunin L, Weaver EJ, et al. Monitoring cerebral function: clinical experience with new device for continuous recording of electrical activity of brain. BMJ. 1971 Jun;2(5764):736–8.

9 Hellström-Westas L, Rosén I, de Vries LS, Greisen G. Amplitude-integrated EEG classification and interpretation in preterm and term infants. Neoreviews. 2006;7(2):e76–87.

10 Olischar M, Klebermass K, Waldhoer T, Pollak A, Weninger M. Background patterns and sleep-wake cycles on amplitude-integrated electroencephalography in preterms younger than 30 weeks gestational age with peri-/intraventricular haemorrhage. Acta Paediatr. 2007 Dec;96(12):1743–50.

11 Pisani F, Copioli C, Turco EC, Sisti L, Cossu G, Seri S. Mortality risk after neonatal seizures in very preterm newborns. J Child Neurol. 2012 Oct;27(10):1264–9.

12 Pisani F, Facini C, Pelosi A, Mazzotta S, Spagnoli C, Pavlidis E. Neonatal seizures in preterm newborns: A predictive model for outcome. Eur J Paediatr Neurol. 2016 Mar;20(2):243–51.

13 Wikström S, Pupp IH, Rosén I, Norman E, Fellman V, Ley D, et al. Early single-channel aEEG/EEG predicts outcome in very preterm infants. Acta Paediatr. 2012 Jul;101(7):719–26.

14 Vesoulis ZA, Inder TE, Woodward LJ, Buse B, Vavasseur C, Mathur AM. Early electrographic seizures, brain injury, and neurodevelopmental risk in the very preterm infant. Pediatr Res. 2014 Apr;75(4):564–9.

15 Lloyd RO, O'Toole JM, Pavlidis E, Filan PM, Boylan GB: Electrographic seizures during the early postnatal period in preterm infants. J Pediatr 2017;187:18-25.e12.

16 Davis AS, Hintz SR, Van Meurs KP, Li L, Das A, Stoll BJ, et al. Seizures in extremely low birth weight infants are associated with adverse outcome. J Pediatr 2010;157:720-725 e721-722.

17 Weeke LC, van Ooijen IM, Groenendaal F, van Huffelen AC, van Haastert IC, van Stam C, et al. Rhythmic EEG patterns in extremely preterm infants: classification and association with brain injury and outcome. Clin Neurophysiol. 2017 Dec;128(12):2428–35.