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ARTICLE

# Antecedents of epilepsy and seizures among children born at extremely low gestational age

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## Abstract

**Objective** To identify specific risk factors for epilepsy for individuals born extremely preterm.

**Study Design** In a prospective cohort study, at 10-year follow-up, children were classified as having epilepsy or seizures not associated with epilepsy. We evaluated for association of perinatal factors using time-oriented, multinomial logistic regression models.

**Results** Of the 888 children included in the study, 66 had epilepsy and 39 had seizures not associated with epilepsy. Epilepsy was associated with an indicator of low socioeconomic status, maternal gestational fever, early physiologic instability, postnatal exposure to hydrocortisone, cerebral white matter disease and severe bronchopulmonary dysplasia. Seizure without epilepsy was associated with indicators of placental infection and inflammation, and hypoxemia during the first 24 postnatal hours.

**Conclusions** In children born extremely preterm, epilepsy and seizures not associated with epilepsy have different risk profiles. Though both profiles included indicators of infection and inflammation, the profile of risk factors for epilepsy included multiple indicators of endogenous vulnerability.

## Introduction

An estimated 10.5 million children worldwide have epilepsy [1, 2] and are at high risk for associated adverse neurodevelopmental and behavioral impairments often necessitating specialized services [3]. The prevalence of epilepsy in children ranges from 41 to 187/100,000 with a range of 3.2–5.5/1,000 in developed countries and 3.6–44/1,000 in developing countries [4]. However, these data are a composite of data from children born at term and preterm. The prevalence of seizures and/or epilepsy later in life in children who were born extremely preterm (EP), ranges from 2.2 to 10% [5–7]. This is 5-fold higher in the first year of life and 2.5-fold higher in adolescent and early adulthood years for children born < 33 weeks as compared to infants born at term [8].

Among children born at term, perinatal and neonatal risk factors for epilepsy versus seizures without epilepsy (see case definitions below) include perinatal and post infectious encephalopathy [1], maternal/placental infections [9], placental ischemia [10], and placental inflammation [11]. Prematurity poses an added independent risk for developing epilepsy [12, 13]. Risk factors for brain injury among

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children born EP include a paucity of "developmentally regulated" brain-damage protectants, such as growth factors [14], neurosteroids [15], and anti-inflammatory proteins [16, 17], and frequent occurrence of inflammatory conditions [18], including bacteremia [19], necrotizing enterocolitis [20], and prolonged ventilation [21]. Previous studies of large cohorts of extremely low gestational age newborns (ELGANs) have not provided much information about these risks [22, 23]. With data from our large prospective cohort of the ELGAN Study, we sought to identify potentially modifiable risk factors that predispose children born EP to epilepsy and seizures not associated with epilepsy.

## Methods

### Participants

The ELGAN study is a multi-center observational study designed to identify characteristics and exposures associated with increased risk of structural and functional neurologic disorders in extremely preterm infants [24]. During the years 2002–2004, women delivering before 28 weeks gestation at one of 14 participating institutions were asked to enroll in the study. A total of 1249 mothers of 1506 ELGANs consented to participate. Details about the pregnancy, the mother and the newborn were collected and are found in Appendix A.

Eight-hundred eighty-eight of 966 children for whom we possessed measures of inflammation-related proteins in blood collected during the first postnatal month are the subjects of this report. They underwent assessments of cognition, executive function, behavior, and academic achievement at age 10 years [25].

Enrollment and consent procedures for both phases of the study were approved by the institutional review boards of all participating institutions.

### Seizure assessment

Identification of children with seizures or epilepsy involved a two stage process [5]. At the time, the child was brought for the 10-year follow-up assessment, a research assistant asked the parent 11 broad questions about any possible seizures since discharge from the NICU. A yes response to any of these questions prompted a pediatric epileptologist to schedule a structured telephone interview to determine whether a reported event was indeed a seizure. A second pediatric epileptologist independently reviewed interview responses and similarly rated the event type. When the two epileptologists disagreed on the presence of seizures, a third pediatric epileptologist reviewed the interview responses and made the final seizure determination. All three pediatric epileptologists are board-certified in child neurology and in epilepsy or neurophysiology, and all have more than 20 years of clinical epilepsy experience. While desirable as gold standard for confirmed diagnosis of seizures or epilepsy, electroencephalography (EEG) or video-EEGs were not performed during the study visits. Our longitudinal design did not include collection of EEG.

Forty-three of 273 children who screened at risk for seizures could not be contacted for full evaluation by the epileptologist. We imputed seizure case/control status and seizure type for these 43 children within strata of sex and gestational age, applying the cumulative prevalence seen among the 230 children who were screened at risk and whose parents participated in the full evaluation using inverse probability weighting. A total of 14 cases were imputed for the purposes of analysis −9 in the epilepsy group and 5 in the seizures not associated with epilepsy group.

### Case definitions

We used a modified version of the 2014 International League Against Epilepsy's (ILAE) definition of epilepsy. In 2014, the ILAE defined epilepsy as at least two unprovoked seizures occurring >24 h apart or one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next ten years. It was not possible to know the recurrence risk following a single seizure with the methodology used for this study, and thus the definition was simplified. Epilepsy was defined as two or more seizures, separated by 24 h, after discharge from the NICU not associated with fever, trauma, or acute infection of the central nervous system.

Unprovoked seizure (i.e., hereafter, "seizure without epilepsy") was defined as occurrence of a single seizure that was not associated with fever, trauma, or infection of the central nervous system.

### Data analysis

We did not calculate sample size requirements a priori. Rather, we decided we had appreciable power when we saw that an exposure in a quarter of the sample could be associated with statistically significant doubling of epilepsy risk. We evaluated the generalized form of the null hypothesis that epilepsy as well as seizures without epilepsy are not associated with maternal, pregnancy, delivery, or postnatal characteristics and exposures. We began with univariate analyses (Tables 1–3, and Supplementary Tables A1–A5 in

**Table 1** Row percents of maternal demographic characteristics of children who had epilepsy, seizures not associated with epilepsy, and no seizures

| Maternal characteristic | Epilepsy | Seizures not associated with epilepsy | No seizures | Row N |
|---|---|---|---|---|
| Racial identity | | | | |
| White | 6 | 4 | 90 | 562 |
| Black | 11 | 4 | 85 | 227 |
| Other | 8 | 5 | 87 | 97 |
| Hispanic | | | | |
| Yes | 9 | 6 | 85 | 85 |
| No | 7 | 4 | 89 | 801 |
| Maternal age, years | | | | |
| <21 | 10 | 6 | 84 | 114 |
| 21–35 | 7 | 4 | 89 | 594 |
| >35 | 6 | 6 | 88 | 180 |
| Years of education | | | | |
| ≤12 (HS) | 11 | 5 | 84 | 367 |
| >12 to <16 | 7 | 5 | 89 | 209 |
| ≥16 (College) | 4 | 4 | 93 | 312 |
| Single? | | | | |
| Yes | 10 | 5 | 85 | 352 |
| No | 6 | 4 | 90 | 536 |
| Self-supported? | | | | |
| Yes | 6 | 4 | 90 | 581 |
| No | 10 | 6 | 84 | 292 |
| Public insurance | | | | |
| Yes | 12 | 5 | 83 | 313 |
| No | 5 | 4 | 91 | 575 |
| Pre-pregnancy | | | | |
| <18.5 | 9 | 4 | 87 | 68 |
| Body Mass | | | | |
| 18.5, <25 | 8 | 4 | 88 | 428 |
| Index (BMI) | | | | |
| 25, <30 | 4 | 4 | 92 | 166 |
| >30 | 9 | 6 | 85 | 194 |
| **Total row percent** | 7 | 4 | 88 | |
| **Maximum column *N*** | 66 | 39 | 783 | 888 |

Appendix A), which identified candidate variables for logistic regression analyses.

Because postnatal phenomena, such as the need for ventilatory assistance, can be influenced by antepartum phenomena, we created logistic regression models in which risk factors are ordered in a temporal pattern, so that the earliest occurring predictors/covariates of epilepsy or seizures without epilepsy were entered first and were not displaced by later occurring covariates. For these time-oriented multivariable risk models (TORMs), we categorized sets of antecedents/covariates as either antenatal, first 24 h postnatal, early postnatal, or late postnatal. Each set is called an epoch (Table 4).

Because our outcomes of interest are mutually exclusive and each is appropriately compared to the same referent group (of children who had neither epilepsy nor seizures

**Table 2** Row percents of placenta characteristics of children who had epilepsy, seizures not associated with epilepsy, and no seizures

| | Epilepsy | Seizures not associated with epilepsy | No seizures | Row N |
|---|---|---|---|---|
| *Placenta microbiology* | | | | |
| # of species isolated | | | | |
| 0 | 7 | 3 | 90 | 399 |
| 1 | 8 | 4 | 88 | 207 |
| ≥2 | 10 | 9 | 82 | 200 |
| Aerobe | | | | |
| Yes | 8 | 7 | 85 | 265 |
| No | 7 | 4 | 89 | 541 |
| Anaerobe | | | | |
| Yes | 10 | 7 | 83 | 229 |
| No | 7 | 4 | 89 | 577 |
| Mycoplasma | | | | |
| Yes | 5 | 10 | 85 | 80 |
| No | 8 | 4 | 88 | 726 |
| Skin organisms[a] | | | | |
| Yes | 8 | 9 | 83 | 163 |
| No | 7 | 4 | 89 | 643 |
| Vaginal organisms[b] | | | | |
| Yes | 9 | 8 | 83 | 129 |
| No | 7 | 4 | 88 | 677 |
| **Total row percent** | 8 | 5 | 88 | |
| **Maximum column *N*** | 61 | 39 | 706 | 806 |
| *Placenta histology* | | | | |
| Chorionic plate inflammation[c] | | | | |
| Yes | 8 | 9 | 82 | 154 |
| No | 8 | 3 | 89 | 663 |
| Chorion/decidua inflammation[d] | | | | |
| Yes | 8 | 6 | 87 | 287 |
| No | 7 | 4 | 89 | 530 |
| Fetal stem vessel Infiltration | | | | |
| Yes | 8 | 7 | 85 | 204 |
| No | 7 | 4 | 89 | 609 |
| Umbilical cord vasculitis[e] | | | | |
| Yes | 8 | 8 | 84 | 132 |
| No | 7 | 4 | 89 | 668 |
| Fetal stem vessel thrombosis | | | | |
| Yes | 7 | 7 | 85 | 41 |
| No | 8 | 4 | 88 | 771 |
| Infarct | | | | |
| Yes | 6 | 4 | 90 | 146 |
| No | 8 | 4 | 88 | 679 |
| Increased syncytial Knots | | | | |
| Yes | 7 | 3 | 90 | 165 |
| No | 8 | 5 | 87 | 663 |
| Decidual hemorrhage/fibrin deposition | | | | |
| Yes | 9 | 2 | 89 | 139 |
| No | 7 | 5 | 88 | 667 |
| **Total row percent** | 8 | 4 | 88 | |
| **Maximum column *N*** | 63 | 36 | 729 | 828 |

[a]Corynebacterium sp, Propionebacterium sp, Staphylococcus sp

[b]Prevotella bivia, Lactobacillus sp, Peptostrep magnus, Gardnerella vaginalis

[c]stage 3 and severity 3

[d]grades 3 and 4

[e]grades 3, 4 and 5

without epilepsy), we created time-oriented multinomial logistic models using a step-down procedure, seeking a parsimonious solution without interaction terms [26]. The strength of association for relevant variables is presented as a risk ratio with its 95% confidence interval. For comparison, we also conducted a "standard" (not time-oriented) multinomial multivariate logistic regression analysis. For the standard analysis, all the predictors/covariates were entered at the same time, with no regard to when they occurred, and a parsimonious solution was found using a step-down procedure. (Table 5)

## Results

Of the 888 children screened for seizures, 66 were identified as having epilepsy, while 39 were identified as having seizures without epilepsy. These children were compared with the 783 children who had neither. The univariate analyses of specific risk factors identified the variables for inclusion in the logistic regression analyses. Some of these data are presented in Tables 1–3 and the relevant text and related tables describing them are included in Appendix A.

### Maternal characteristics

Children whose mother had no more than a high school education, were not married, and/or were eligible for government-provided insurance at the time of delivery were more likely than others to develop epilepsy, but not more likely to experience seizures without epilepsy (Table 1).

### Placenta characteristics

Children whose placenta harbored an anaerobe were more likely than others to have epilepsy, while those children whose placenta harbored more than one microbe or Mycoplasma were more likely than others to have seizures without epilepsy (Table 2).

### Postnatal diagnoses and conditions

Infants were more likely than others to develop epilepsy if they had intraventricular hemorrhage (IVH), white matter disease (WMD), a growth velocity during the first postnatal 28 days that was in the lowest quartile, pneumothorax, or required ventilator and supplemental oxygen during the 36th week of corrected gestational age. Infants were more likely than others to develop seizures without epilepsy (but not epilepsy) if they had WMD or necrotizing enterocolitis (NEC) requiring surgery (Table 3).

**Table 3** Row percents of postnatal characteristics and diagnoses of children who had epilepsy, seizures not associated with epilepsy, and no seizures

| Postnatal diagnoses and conditions | Epilepsy | Seizures not associated with epilepsy | No seizures | Row N |
|---|---|---|---|---|
| Intraventricular hemorrhage[a] | | | | |
| Yes | 13 | 6 | 81 | 191 |
| No | 6 | 4 | 90 | 697 |
| Cerebral white matter disease[b] | | | | |
| Echolucency with/without ventriculomegaly | 30 | 7 | 63 | 56 |
| Ventriculomegaly only | 12 | 10 | 78 | 67 |
| Neither echolucency nor ventriculomegaly | 5 | 4 | 91 | 765 |
| Lowest quartile growth velocity[c] | | | | |
| Yes | 10 | 2 | 88 | 204 |
| No | 7 | 5 | 88 | 658 |
| Patent ductus arteriosus[d] | | | | |
| Yes | 7 | 4 | 89 | 602 |
| No | 9 | 5 | 86 | 286 |
| Pneumothorax | | | | |
| Yes | 10 | 4 | 86 | 72 |
| No | 7 | 4 | 88 | 816 |
| PIE[e] | | | | |
| Yes | 9 | 4 | 87 | 148 |
| No | 7 | 4 | 88 | 740 |
| Pulmonary hemorrhage | | | | |
| Yes | 3 | 3 | 94 | 31 |
| No | 8 | 4 | 88 | 857 |
| Respiratory group classification | | | | |
| EPPD[f] | 9 | 4 | 87 | 365 |
| PD[g] | 7 | 6 | 87 | 323 |
| Low $FiO_2$ | 4 | 2 | 94 | 175 |
| Necrotizing enterocolitis (Bell stage) | | | | |
| <IIIb[h] | 8 | 4 | 88 | 827 |
| IIIb | 9 | 9 | 81 | 32 |
| Isolated perf[i] | 0 | 3 | 97 | 29 |
| ROP: stage | | | | |
| 3–5 | 9 | 4 | 88 | 253 |
| <3 | 7 | 5 | 88 | 621 |
| ROP: plus plus disease | | | | |
| Yes | 8 | 5 | 86 | 96 |
| No | 7 | 4 | 88 | 778 |
| ROP: Pre-threshold[j] | | | | |
| Yes | 9 | 4 | 87 | 117 |
| No | 7 | 4 | 88 | 757 |
| BPD/CLD | | | | |
| On vent[k] | 20 | 4 | 76 | 80 |
| Off vent[l] | 7 | 5 | 88 | 380 |
| No | 5 | 4 | 94 | 421 |
| **Total row percent** | 7 | 4 | 88 | |
| **Maximum column *N*** | 66 | 39 | 783 | 888 |

[a]Alone or with other lesions

[b]Defined as an echolucent lesion on cranial ultrasound during the NICU stay. Alone or with other lesions

[c]$1000 \times ((wt28 - wt7) / wt7)/21$; units: g/kg/day

[d]Clinical diagnosis with/without echocardiogram; All infants included irrespective of need for treatment

[e]Pulmonary interstitial emphysema

[f]Early and persistent pulmonary dysfunction

[g]Pulmonary deterioration

[h]Includes less severe disease

[i]Isolated intestinal perforation

[j]Satisfied ET-ROP criteria for ablative surgery (pre-threshold disease)

[k]On ventilator as well as oxygen at 36 weeks post-menstrual age

[l]On oxygen, but not on ventilator at 36 weeks post-menstrual age

## Time-oriented Multivariable Risk Models

Of the antenatal epoch variables assessed, only mother's eligibility for government-provided (public) health care insurance (Medicaid) (Odds ratios = 2.7; 95% confidence interval: 1.6, 4.5) and mother's fever during the pregnancy (OR = 2.5; 95% CI: 1.1, 5.8) were associated with an elevated risk of epilepsy (Table 4). The other two first epoch variables, "≥2 organisms in placenta" and "chorionic plate inflammation" are included in the multinomial model because they provide risk information about seizures not associated with epilepsy.

When variables from the first 24 h postnatal epoch were considered, only one, top quartile of the difference between the lowest and highest mean arterial pressure (OR = 2.2; 95% CI: 1.3, 3.8), was added to the antenatal epoch logistic regression model. Of the variables considered in the early postnatal epoch (the rest of the first postnatal month), three variables added risk information: lowest quartile PCO2, (OR = 2.1; 95% CI: 1.1, 3.7), ventilated on day 14 (OR = 2.3; 95% CI: 1.2, 4.5), and white matter disease (OR = 6.3; 95% CI: 3.1, 13). The only variable from the late postnatal epoch (after the first postnatal month and before discharge from the hospital) that added risk information was severe bronchopulmonary dysplasia/chronic lung disease, defined as requiring ventilator support and supplemental oxygen during the 36th week post menstruation (OR = 4.5; 95% CI: 2.2, 9.2).

Of all antenatal variables, only two characteristics of the placenta provided information about an increased risk of seizures without epilepsy: recovery of two or more organisms from the placenta, (OR = 2.4; 95% CI: 1.2, 4.7) and

**Table 4** Time-oriented Multinomial (polytomous) multi-variable-Adjusted Odds Ratios (Point estimates and 95% CIs) for having epilepsy or seizures not associated with epilepsy associated with each antenatal, neonatal, postnatal, and late postnatal risk factors entered into the model by epoch

| | Epoch | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Epilepsy | | | | Seizures not associated with epilepsy | | | |
| Variables | Antenatal | First 24 h Postnatal | Early postnatal | Late postnatal | Antenatal | First 24 h Postnatal | Early postnatal | Late postnatal |
| *Antenatal epoch* | | | | | | | | |
| Public insurance | **2.7 (1.6, 4.5)** | **2.5 (1.5, 4.2)** | **2.3 (1.3, 4.0)** | **2.4 (1.4, 4.3)** | 1.3 (0.7, 2.5) | 1.3 (0.7, 2.5) | 1.3 (0.6, 2.6) | 1.3 (0.6, 2.6) |
| Fever >100.4 F in pregnancy | **2.5 (1.1, 5.8)** | **2.5 (1.1, 5.8)** | **2.6 (1.1, 6.2)** | **3.0 (1.2, 7.4)** | 1.1 (0.2, 4.7) | 1.1 (0.2, 4.7) | 1.0 (0.2, 4.6) | 1.0 (0.2, 4.5) |
| ≥2 organisms in placenta | 1.5 (0.8, 2.6) | 1.4 (0.8, 2.6) | 1.1 (0.7, 2.7) | 1.2 (0.6, 2.3) | **2.4 (1.2, 4.7)** | **2.4 (1.2, 4.7)** | **2.4 (1.2, 4.8)** | **2.4 (1.2, 4.9)** |
| Chorionic plate inflammation[a] | 1.2 (0.6, 2.3) | 1.3 (0.6, 2.4) | 1.4 (0.7, 2.7) | 1.5 (0.7, 3.0) | **2.6 (1.3, 5.4)** | **2.7 (1.3, 5.4)** | **2.8 (1.4, 6.0)** | **2.8 (1.4, 6.0)** |
| *Neonatal epoch* | | | | | | | | |
| Labile MAP first 24 h[b] | | **2.2 (1.3, 3.8)** | **2.2 (1.2, 3.8)** | **2.3 (1.3, 4.1)** | | 1.3 (0.6, 2.7) | 1.3 (0.6, 2.8) | 1.3 (0.6, 2.8) |
| *Early postnatal epoch* | | | | | | | | |
| Lowest Q lowest $P_aO_2$[c] | | | 1.4 (0.7, 2.7) | 1.3 (0.7, 2.7) | | | **2.9 (1.3, 6.5)** | **2.8 (1.2, 6.3)** |
| Lowest Q lowest $PCO_2$[c] | | | **2.0 (1.1, 3.7)** | **2.0 (1.05, 3.8)** | | | 1.4 (0.6, 3.4) | 1.4 (0.6, 3.4) |
| Mechanical ventilation, day 14 | | | **2.3 (1.2, 4.5)** | 1.6 (0.8, 3.2) | | | 1.4 (0.6, 2.8) | 1.3 (0.6, 2.8) |
| Cerebral white matter disease[d] | | | **6.3 (3.1, 13)** | **7.7 (3.6, 16)** | | | 2.0 (0.6, 6.3) | 1.8 (0.6, 5.8) |
| *Late postnatal epoch* | | | | | | | | |
| Severe BPD/CLD | | | | **4.5 (2.2, 9.2)** | | | | 1.0 (0.3, 3.5) |

[a]Stage 3 and severity 3

[b]Labile MAP: labile blood pressure, defined as the upper quartile of the difference in the lowest and highest MAP

[c]Extreme quartile for gestational age on two of the first three postnatal days.

[d]Defined as an echolucent lesion on cranial ultrasound during the NICU stay. Alone or with other lesions

Statistically significant values are in bold

chorionic plate inflammation (OR = 2.2; 95% CI: 1.3, 3.8). Although no first 24 h postnatal epoch variable added risk information, one variable from the early postnatal epoch, lowest quartile PaO2 during two of the first three postnatal days, did (OR = 2.9; 95% CI: 1.3, 6.5). No late postnatal epoch variable added discriminating information about the risk of seizures without epilepsy.

### Standard multivariable model

Variables associated with risk of epilepsy are public insurance, fever >100.4 F during pregnancy, labile mean arterial pressure (MAP) in the first 24 postnatal hours, lowest quartile of the lowest PaCO2, receipt of hydrocortisone in the first postnatal month, white matter disease on cranial ultrasound, and severe bronchopulmonary dysplasia/chronic lung disease. Variables associated with seizures not associated with epilepsy are recovery of two or more organisms from the placenta, chorionic plate inflammation, and lowest quartile PaO2 during two of the first three postnatal days (Table 5).

Although early-occurring variables are not displaced by those that occur later in the TORM, this is not the case in the standard multivariate model. The standard model identified hydrocortisone, an early postnatal epoch variable rather than mechanical ventilation on day 14, and this may account for the small changes in the ORs and 95% confidence intervals.

**Table 5** Standard Multinomial (polytomous) multi-variable-Adjusted Odds Ratios (Point estimates and 95% CIs) for having epilepsy or seizures not associated with epilepsy associated with predictors/confounders

| Variables | Epilepsy | Seizures not associated with epilepsy |
|---|---|---|
| Public insurance | **2.5 (1.4, 4.4)** | 1.3 (0.6, 2.6) |
| Fever >100.4 F in pregnancy | **3.1 (1.3, 7.7)** | 1.1 (0.3, 4.9) |
| ≥2 organisms in placenta | 1.3 (0.7, 2.4) | **2.4 (1.2, 4.7)** |
| Chorionic plate inflammation[a] | 1.5 (0.7, 3.0) | **2.9 (1.4, 6.2)** |
| Labile MAP first 24 h[b] | **2.3 (1.3, 4.2)** | 1.2 (0.6, 2.7) |
| Lowest Q lowest $P_aO_2$[c] | 1.3 (0.6, 2.7) | **2.8 (1.3, 6.4)** |
| Lowest Q lowest $PCO_2$[c] | **2.1 (1.1, 4.1)** | 1.5 (0.6, 3.5) |
| Any hydrocortisone | **2.1 (1.05, 4.2)** | 2.2 (0.9, 5.2) |
| Cerebral White Matter Disease[d] | **8.1 (3.8, 17)** | 2.0 (0.6, 6.3) |
| Severe BPD/CLD | **5.1 (2.6, 10)** | 1.1 (0.3, 3.9) |

[a]Stage 3 and severity 3

[b]Labile MAP: labile blood pressure, defined as the upper quartile of the difference in the lowest and highest MAP

[c]Extreme quartile for gestational age on two of the first three postnatal days

[d]Defined as an echolucent lesion on cranial ultrasound during the NICU stay. Alone or with other lesions

Statistically significant values are in bold

## Discussion

Children in our ELGAN Study cohort have a higher prevalence of both epilepsy and seizures without epilepsy than is reported for children born at term [5, 27]. In this study, we demonstrate two key points about the risk profile for epilepsy and seizures without epilepsy. First, both epilepsy and seizures without epilepsy have common risk themes: illness severity, markers of inflammation and markers of infection. Second, the timing of exposure for these were in distinct epochs with virtually no overlap.

To our knowlege this is the first, large epidemiological study of ELGANs describing the risk factors for later development of epilepsy and seizures not associated with epilepsy. ELGANs who subsequently developed epilepsy were more likely than others to be born to mothers of low socioeconomic status (SES) and who had at least one documented fever > 100.4 during pregnancy.

The ELGANs themselves were more likely than their peers to have had clinical evidence of early labile mean arterial blood pressure (MAP), low $PaCO_2$, higher SNAP-II scores, need for mechanical ventilation as late as day 14, white matter disease (WMD) and severe bronchopulmonary dysplasia (BPD).

In contrast, ELGANs who had seizures without epilepsy were more likely than others to have had a placenta that harbored a microbial colonization, and had inflammation of the chorionic plate and themselves had a low $PaO_2$.

### Socioeconomic Status

ELGANs born to mothers with low SES, defined by eligibility for government-provided medical care insurance, were more than twice as likely as others of developing childhood-onset epilepsy, but were not at increased risk for having seizures without epilepsy. Low maternal SES is a correlate of epilepsy in children born at term, though the reasons for this are unclear [28]. While specific factors associated with low SES such as maternal smoking, have been associated with febrile seizures [29, 30], we found no reported associations with epilepsy. In high income countries, children in low SES families are at heightened risk of chronic debilitating illnesses, including epilepsy [31]. Low maternal SES is also associated with preterm labor and preterm births [32], both of which are associated with increased risk of adverse neurodevelopmental outcomes [33]. In addition, poverty is associated with underdevelopment of the gray matter of children; [34] these structural differences may be among the many factors that place children of low SES at risk for seizures and other neurodevelopmental disorders.

## Infection and Inflammation

### Association of Infection and Inflammation with Epilepsy

Inflammation has been linked with epilepsy and/or seizures in animal models and in children [35, 36]. Inflammatory proteins, microglial and astrocyte activation, and cellular injury are abundant in resected epileptogenic zones of children with intractable epilepsy [37]. Demonstrating a causal inflammatory pathway that leads to epileptogenesis, however, is more difficult as most studies identify inflammation only after seizures develop. A strength of the ELGAN cohort is the availability of placental biomarkers and clinical indicators of inflammation and infection prior to seizure or epilepsy onset.

We found a risk association between perinatal infection, inflammation, and later development of epilepsy. Mothers who developed any fever >100.4 °F during the course of pregnancy had almost 3 times greater risk of having children with childhood-onset epilepsy. Others have reported that maternal infection before, but not during pregnancy was associated with an increased risk of epilepsy [38]. Placental inflammation (identified as chorioamnionitis) has been associated with an increased risk of epilepsy in term infants [39] and seizures (before the second birthday) among very low birth weight infants [40]. Maternal fever with potential fetal exposure to both microbial agents as well as maternal markers of inflammation, may lead to a more generalized systemic inflammatory response in the fetus [41]. While neuronal inflammation can be either a contributor to, or a consequence of seizures [42], because maternal infection in our cohort pre-dates seizure onset, inflammation is more likely to be a cause rather than a consequence of seizures.

### Association of Infection and Inflammation with Seizures Without Epilepsy

We found that children whose placenta harbored multiple organisms and those whose placenta was inflamed were at 2.4 to 3 fold increased risk of seizures not associated with epilepsy. Inflammation can alter brain growth [43], increase neuronal excitability and lower the seizure threshold [35, 36, 38]. In this cohort, polymicrobial infections of the placenta also were associated with increased risk of ventriculomegaly and echolucent lesions on brain ultrasonography, as well as diparetic cerebral palsy [44]. Consequently, we view polymicrobial infections as biologically important and not just an indicator of contamination.

## Illness In The Neonatal Period

### Association of Illness and Epilepsy

Meticulous adherence to best practices during the interval between birth and the first sixty minutes of life is associated with shorter length of stay, and a lower incidence of BPD and IVH among ELGANs [45, 46]. This leads to the possibility that such care might reduce the incidence of epilepsy if the care of MAP lability, hypocarbia and other correlates of physiologic instability are optimized. The vulnerability of the brain to hemodynamic factors can vary to some extent with the stage of oligodendroglial maturation [47] and with the ability of the brain to synthesize adequate amounts of neurotrophins [48]. Consequently, we are unable to distinguish between causal contributions of these antecedents to the occurrence of epilepsy and the information they provide about immaturity/vulnerability that supplements such information conveyed by low gestational age. Data from studies of term infants with brain injury supports the detrimental impact of hypocarbia on long term neurodevelopmental outcomes, probably due to decreased cerebral blood flow, alterations in cellular and oxygen metabolism, and impaired ability to clear neurotoxic metabolites [49, 50]. For ELGANs, prevention and early treatment of hypocarbia and labile blood pressure, both markers of illness severity with need for respiratory support, may help decrease the incidence of childhood-onset of epilepsy.

The need for mechanical ventilation at day 14 with a subsequent diagnosis of severe BPD/CLD, defined by the need for ventilation assistance during the 36th postmenstrual week, and any receipt of postnatal hydrocortisone were associated with increased risk of childhood-onset epilepsy. Severe BPD/CLD, also an inflammatory disorder [21], might be either in the causal chain leading to epilepsy or represent an indicator of immaturity and endogenous vulnerability. We posit that infants with severe parenchymal lung disease are a sicker group of infants than those without lung disease and are more susceptible to inflammatory and other risks leading to abnormal brain function and development. Persistent prolonged oxygen exposure in infants with severe BPD with limited anti-oxidative capabilities places actively proliferating neuronal cells at greater risk of free oxygen radical injury [51]. Although any hydrocortisone use was associated with an increased risk of epilepsy in the standard multinomial model, the association did not hold true in the TORM suggesting that hydrocortisone use correlates with earlier occurring exposures or characteristics identified in the TORM, or with other risk factors that convey information about hydrocortisone exposure and other exposures/characteristics.

### Association of illness and seizures without epilepsy

The time-oriented models not only raise concern that outcomes in ELGANs are impacted by a continuum of exposures, but also point to potential clinical strategies to mitigate the onset of epilepsy and seizures without epilepsy. In particular, children with epilepsy were exposed to multiple antenatal, as well as early and late adverse neonatal risks. By comparison, seizures not associated with epilepsy occurred in infants with overall less severe morbidities during their initial NICU hospitalization.

## Head ultrasound abnormalities

### Association of head ultrasound with epilepsy

WMD was the strongest predicator of childhood-onset epilepsy in ELGANs, with an almost 8-fold increase in odds ratio. Infants with structural brain diseases including periventricular leukomalacia are known to be at high risk for intractable epilepsy [52] The finding that both cerebral palsy and epilepsy can be consequences of PVL [53] suggests the involvement of both gray matter damage (providing a possible site for cortical excitability and seizure generation) and white matter damage (impairing mechanisms to control the spread of epileptic discharges) [54]. WMD was not associated with a higher risk of seizures without epilepsy in our cohort.

## Strengths/Limitations

Our study's major strength is the prospective design of this large multicenter cohort with the early collection of information about antecedents and follow-up years later, especially with relatively little loss of follow-up. We acknowledge that lack of real time EEG data is a limitation of our study but the two-step validated questionnaire with a follow-up in depth clinical interview with a pediatric epileptologist provided confidence in the accuracy of the parent-reported data [5]. The follow-up rate for confirmation of the primary outcomes for our study was 84% and while a more robust follow-up is desired, attrition in longitudinal follow-up studies is unavoidable. Additional, limitations include our lack of data about seizures that may have occurred during the NICU hospitalization.

# Conclusion

Among children born extremely preterm epilepsy and seizures without epilepsy have common risk themes: illness severity, markers of inflammation and markers of infection. The epilepsy profile, however, includes multiple indicators of endogenous vulnerability, while the profile of seizure without epilepsy does not. The ability to identify the at-risk infant may allow better prognostication and facilitate earlier identification and treatment of epilepsy or seizures in the ELGAN population. Future studies should focus on identifying the potentially modifiable maternal and neonatal factors that might reduce the occurrence of epilepsy for children born extremely preterm.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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