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Original Article

Characterization of Death in Infants With Neonatal Seizures

Monica E. Lemmon, MD [a, *], Sonia L. Bonifacio, MD [b], Renée A. Shellhaas, MD, MS [c], Courtney J. Wusthoff, MD, MS [b, d], Rachel G. Greenberg, MD, MB, MHS [a, e], Janet S. Soul, MDCM [f], Taeun Chang, MD [g], Catherine J. Chu, MD [h], Sara Bates, MD [i], Shavonne L. Massey, MD [j], Nicholas S. Abend, MD, MSCE [j, k], M. Roberta Cilio, MD, PhD [l], Hannah C. Glass, MDCM [m, n, o], on behalf of the Neonatal Seizure Registry

[a] *Departments of Pediatrics and Population Health Sciences, Duke University School of Medicine, Durham, North Carolina*
[b] *Department of Pediatrics, Stanford University, Palo Alto, California*
[c] *Department of Pediatrics, University of Michigan, Ann Arbor, Michigan*
[d] *Department of Neurology, Stanford University, Palo Alto, California*
[e] *Duke Clinical Research Institute, Durham, North Carolina*
[f] *Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts*
[g] *Department of Neurology, Children's National Hospital, George Washington University School of Medicine, Washington, District of Columbia*
[h] *Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts*
[i] *Department of Pediatrics, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts*
[j] *Departments of Neurology and Pediatrics, Children's Hospital of Philadelphia and Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania*
[k] *Department of Anesthesia & Critical Care Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania*
[l] *Department of Pediatrics, Saint-Luc University Hospital, Catholic University of Louvain, Brussels, Belgium*
[m] *Department of Pediatrics, UCSF Benioff Children's Hospital, University of California San Francisco, San Francisco, California*
[n] *Department of Epidemiology & Biostatistics, University of California San Francisco, San Francisco, California*
[o] *Department of Neurology, UCSF Benioff Children's Hospital, University of California San Francisco, San Francisco, California*

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ABSTRACT

Background: Neonatal seizures are associated with death and neurological morbidity; however, little is known about how neonates with seizures die.
Methods: This was a prospective, observational cohort study of neonates with seizures treated at seven sites of the *Neonatal Seizure Registry*. We characterized the mode of death, evaluated the association between infant characteristics and mode of death, and evaluated predictors of death or transfer to hospice.
Results: We enrolled 611 consecutive neonates with seizures, and 90 neonates (15%) died before hospital discharge at a median age of 11 days (range: 1 to 163 days); 32 (36%) died in the first postnatal week. An additional 19 neonates (3%) were transferred to hospice. The most common mode of in-hospital death was death after extubation amidst concerns for poor neurological prognosis, in the absence of life-threatening physiologic instability (n = 43, 48%). Only one infant died while actively receiving cardiopulmonary resuscitation. In an adjusted analysis, premature birth (odds ratio: 3.06, 95% confidence interval 1.59 to 5.90) and high seizure burden (odds ratio: 4.33, 95% confidence interval 1.88 to 9.95) were associated with increased odds of death or transfer to hospice.
Conclusion: In a cohort of neonates with seizures, death occurred predominantly after decisions to withdraw or withhold life-sustaining intervention(s). Future work should characterize how these decisions occur and develop optimized approaches to support families and clinicians caring for newborns with seizures.

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* Communications should be addressed to: Dr. Lemmon; Duke University School of Medicine; 2301 Erwin Dr; Durham, NC 27710.
E-mail address: monica.lemmon@duke.edu (M.E. Lemmon).

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Introduction

Seizures are the most common manifestation of neurological dysfunction in newborns and are often the presenting feature of neonatal brain injury.[1] Neonates who experience seizures are at high risk for mortality and morbidity; up to one-third of infants with neonatal seizures die, and survivors are at risk for long-term neurodevelopmental impairment and epilepsy.[2,3] Neonatal seizures arise from heterogeneous etiologies including brain malformations and hypoxic-ischemic encephalopathy (HIE), which confer a high risk of death.[4]

Mortality rates do not reveal the circumstances that surround infant death. Some infants may die in the setting of multiple medical comorbidities and systemic physiologic instability, whereas others may die after clinicians and parents decide to withdraw or withhold life-sustaining treatment in the face of the infant's neurological prognosis. Understanding how infants die—whether death occurred regardless of life-sustaining interventions or instead occurred after parents and clinicians made a decision to limit interventions in the setting of the infant's neurological prognosis—is critically important as clinicians consider how to best counsel and support families of newborns with seizure etiologies or comorbidities that confer poor outcomes. Understanding detailed information about death in neonatal seizures is also necessary for the design and interpretation of studies that use mortality as an outcome. Mortality rates alone may obscure important information about how decisions regarding the withdrawal or withholding of life-sustaining treatment contribute to mortality.

In general, most infants who die during their admission to the neonatal intensive care unit do so after life-sustaining treatment is withheld or withdrawn.[5] Existing data from a single-center cohort of neonates with HIE similarly suggest that most infant deaths occur in the setting of elective extubation due to concerns for poor future quality of life.[6] Infants affected by neonatal seizures represent a broad range of neonatal neurological conditions. Despite the high mortality associated with neonatal seizures, little is known about how death occurs in this population.

We aimed to characterize how infants with seizures die, including the timing, location, and mode of death. We hypothesized that infant death would most commonly occur following extubation amidst concerns for poor neurological prognosis, in the absence of life-threatening physiologic instability.

Methods

Study design and participants

This was a prospective, consecutive, observational cohort study of all neonates with seizures treated at the seven sites of the *Neonatal Seizure Registry (NSR)* between 2013 and 2015. All *NSR* sites follow the American Clinical Neurophysiology Society guidelines for continuous electroencephalography in neonates and have a level IV neonatal intensive care unit.[7] The institutional review boards at each site approved the study and granted waivers of informed consent. Characteristics of neonates in the *NSR* cohort have been previously reported, including the clinical characteristics of infants who died among the first 426 infants enrolled.[4,8-10]

Measurements

Seizure burden was defined as either (1) high (status epilepticus, frequent recurrent seizures without status epilepticus, many [≥7] isolated seizures) or (2) low (less than seven seizures). Incomplete response to antiseizure medication was defined as electrographic seizures that recurred more than 30 minutes after administration of an adequate first-line antiseizure medication. Prematurity was defined as gestational age less than 37 weeks.

Mode of death was characterized using an existing paradigm.[6,11] Medical records were reviewed for information regarding (1) life-threatening physiologic instability in the 24 hours before death, (2) mode of death, and (3) palliative care consultation. Life-threatening physiologic instability was defined as either the presence of extracorporeal membrane oxygenation (ECMO) at the time of death or two or more of the following: (1) persistent desaturation despite 100% oxygen on mechanical ventilation, (2) hypotension despite volume infusion and inotropes, (3) protracted bradycardia in the absence of hypothermia treatment, (4) acidosis, or (5) protracted anuria for more than 24 hours. Mode of death was defined as: (1) *unstable* infants who died while receiving cardiopulmonary resuscitation (CPR), (2) *unstable* ventilated infants who died after a decision to withhold CPR, (3) *unstable* infants who died after a decision to extubate, typically to let a moribund child die in their parents' arms, (4) *stable* infants who died after a decision to extubate, typically for quality-of-life reasons, and (5) *stable* infants who died after a decision to withhold or withdraw artificial hydration and/or nutrition.

Analysis

We assessed the number of infants with seizures who died and were transferred to hospice. Infant demographic and clinical characteristics were summarized overall and by group (died versus transferred to hospice) using counts and percentages for categorical variables and medians and ranges for continuous variables. We evaluated the association among infant demographic characteristics, clinical characteristics, and mode of death using Fisher's exact test. We evaluated predictors of death or transfer to hospice using multivariable logistic regression including the following covariates of interest: sex, race, ethnicity, prematurity, seizure etiology (HIE, ischemic stroke, and intracranial hemorrhage), seizure burden, and incomplete response to antiseizure medication. We performed analyses using Stata version 16.0 (College Station, TX). We considered P values < 0.05 significant.

Results

Clinical characteristics

We enrolled 611 consecutive neonates with seizures. Ninety neonates (15%) died before hospital discharge (Table 1). Death occurred at a median age of 11 days (range 1 to 163 days, interquartile range: 4 to 24 days); 32 (36%) died in the first postnatal week (Fig). HIE was the most common seizure etiology among infants who died (n = 47, 52%), followed by intracranial hemorrhage (n = 11, 12%), brain malformations (n = 6, 7%), and central nervous system (CNS) infections (n = 6, 7%). Of patients with neonatal seizures due to HIE, 58 (25%) died or were transferred to hospice. Most neonates with intracranial hemorrhage were premature (n = 6 of 11, 55%).

An additional 19 neonates (3%) from five sites were transferred to hospice (Table 2). Transfer to hospice occurred at a median age of 20 days (range 6 to 196 days, interquartile range 10 to 31). Death was confirmed in eight of these infants. Seven infants were still living at the time of last documentation, and vital status could not be confirmed in four infants. Most infants (n = 11, 58%) transferred to hospice had a diagnosis of HIE.

Of infants who died or were transferred to hospice, most had high seizure burden (89 of 106, 84%) and incomplete response to antiseizure medication (82 of 100, 82%). The percent of neonates with seizures and in-hospital death or transfer to hospice at each individual site ranged from 6% to 28%. In unadjusted analyses, infants with HIE were more likely to die or be transferred to hospice than infants whose seizures resulted from all other etiologies. Infants with high seizure burden and incomplete response to antiseizure medication were also more likely to die or be transferred to hospice ($P < 0.001$). In the multivariable regression analysis, premature birth (odds ratio [OR] 3.06, 95% confidence interval [CI] 1.59 to 5.90) and high seizure burden (OR 4.33, 95% CI 1.88 to 9.95) were associated with increased odds of death or transfer to hospice (Table 3). A primary seizure etiology of ischemic stroke was associated with decreased odds of death or transfer to hospice (OR 0.20, 95% CI 0.06 to 0.72).

TABLE 1.
Characteristics of 90 Neonates With Seizures Who Died In-hospital During the Neonatal Admission

Characteristic	N = 90
Male sex	43 (48)
Gestational age (completed weeks)	
<29	7 (8)
29-32 + 6/7	6 (7)
33-36 + 6/7	16 (18)
≥37	60 (67)
Race	
Caucasian	38 (54)
Black	12 (17)
Asian	6 (8)
Other	15 (21)
Hispanic ethnicity	14 (19)
Diagnosis	
Hypoxic-ischemic encephalopathy	47 (52)
Intracranial hemorrhage	11 (12)
Brain malformation*	6 (7)
CNS infection	6 (7)
Inborn error of metabolism	4 (4)
Ischemic stroke	3 (3)
Neonatal-onset epilepsy	3 (3)
Other	10 (11)
Comorbid conditions	
Congenital heart disease	25 (28)
Congenital diaphragmatic hernia	5 (6)
Dialysis	4 (4)
ECMO	17 (19)
Age at death (days)	11 (1-163)
Palliative care consultation	32 (36)
Physiologic stability at the time of death†	
Life-threatening physiologic instability (total)	47 (52)
Persistent desaturation	15 (17)
Hypotension	43/88 (49)
Bradycardia in the absence of therapeutic hypothermia	11/87 (13)
Protracted anuria	25/89 (28)
Acidosis	5 (6)
ECMO	17 (19)
Mode of death	
Unstable: Died while receiving CPR	1 (1)
Unstable: Died while withholding CPR	9 (10)
Unstable: Died after discontinuation of ECMO	12 (13)
Unstable: Died after extubation to let infant die in parents' arms	25 (28)
Stable: Elective extubation for QOL considerations	43 (48)
Stable: Died after withdrawal of artificial nutrition and hydration	0

Abbreviations:
CNS = Central nervous system
CPR = Cardiopulmonary resuscitation
ECMO = Extracorporeal membrane oxygenation
QOL = Quality of life
Data are presented as n (%) or median (range).
* Brain malformations included holoprosencephaly, lissencephaly, Dandy-Walker malformation, and pachygyria.
† Cardiorespiratory instability was defined as either receipt of extracorporeal membrane oxygenation (ECMO) or two of the following: persistent desaturation despite 100% oxygen on mechanical ventilation, hypotension despite volume infusion and inotropes, protracted bradycardia in the absence of therapeutic hypothermia, or protracted anuria for 24 hours.

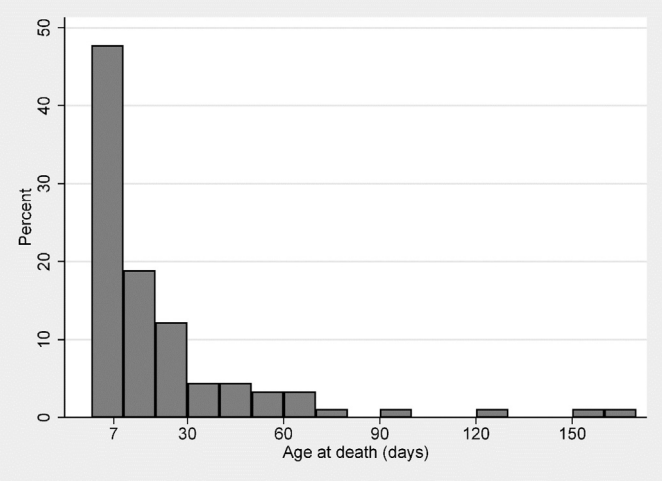

FIGURE. Age at infant death among 90 neonates with seizures.

Mode of death

Approximately half (n = 43 of 90, 48%) of the infants who died in-hospital were physiologically stable at the time of death. Most

TABLE 2.
Characteristics of 19 Infants With Neonatal Seizures Who Were Transferred to Hospice During the Neonatal Admission

Characteristic	N = 19
Male sex	12 (63)
Gestational age (completed weeks)	
<29	1 (5)
29-32 + 6/7	1 (5)
33-36 + 6/7	1 (5)
≥37	16 (84)
Race	
Caucasian	13 (76)
Black	3 (18)
Asian	1 (6)
Other	0 (0)
Hispanic ethnicity	3 (18)
Diagnosis	
Hypoxic ischemic encephalopathy	11 (58)
CNS infection	4 (21)
Brain malformation*	2 (11)
Intracranial hemorrhage	1 (5)
Ischemic stroke	1 (5)
Comorbid conditions	
Congenital heart disease	3 (16)
Congenital diaphragmatic hernia	0 (0)
Dialysis	1 (5)
ECMO	0 (0)
Palliative care consultation	10 (59)
Outcome	
Death confirmed	8 (42)
Still living at time of last documentation	7 (37)
Unknown	4 (21)

Abbreviations:
CNS = Central nervous system
ECMO = Extracorporeal membrane oxygenation
Data are presented as n (%).
* Brain malformations included holoprosencephaly and Dandy-Walker malformation.

TABLE 3.
Clinical Characteristics Associated With Death or Transfer to Hospice on Multivariable Logistic Regression Analysis

Characteristic	Odds Ratio (95% CI)	*P* Value
Male sex	0.71 (0.42-1.20)	0.20
Race and ethnicity		
Caucasian	[Reference]	
Hispanic	0.64 (0.31-1.33)	0.23
Black	0.86 (0.41-1.82)	0.70
Asian	0.64 (0.20-1.98)	0.24
Prematurity	3.06 (1.59-5.90)	0.001
Etiology		
Hypoxic-ischemic encephalopathy	1.41 (0.77-2.57)	0.27
Ischemic stroke	0.20 (0.06-0.72)	0.01
Intracranial hemorrhage	0.81 (0.35-1.87)	0.62
Seizure severity		
High seizure burden	4.33 (1.88-9.95)	0.001
Incomplete response to antiseizure medication	1.34 (0.59-3.02)	0.49

Abbreviation:
CI = Confidence interval

in-hospital deaths occurred after a decision to extubate (n = 68 of 90, 76%). The most common mode of in-hospital death was death in *stable* infants who died after a decision to extubate (n = 43/90, 48%). Twelve children (13%) died following a decision to discontinue ECMO. Of these 12 infants, most were born at term (n = 8, 67%), died after seven days of age (n = 8, 67%), and had a primary diagnosis of HIE (n = 10, 83%). Only one infant died while actively receiving CPR. Although detailed information regarding mode of death was not available for all infants transferred to hospice, three infants who were transferred to hospice ultimately died after a decision to withhold or withdraw artificial hydration and nutrition. All these infants had a diagnosis of HIE and were treated at the same institution.

In HIE, death typically occurred in *stable* infants, who died after a decision to extubate ($P = 0.026$). Other neonatal seizure etiologies were not associated with a particular mode of death. High seizure burden was associated with physiologic instability ($P = 0.012$). Most infants with low seizure burden who died were *stable* infants who died after a decision to extubate ($P = 0.045$). Infant sex, gestational age, race, and ethnicity were not associated with mode of death.

Palliative care

Palliative care service utilization was higher among infants who were transferred to hospice (n = 10 of 17, 59%), compared with those who died in the hospital (n = 32 of 90, 36%), although the difference was not statistically significant ($P = 0.1$). The involvement of palliative care team support was associated with mode of death and was most common for *unstable* infants who died after a decision to withhold CPR, followed by *stable* infants who died after a decision to extubate ($P < 0.001$). No infants who died after a decision to discontinue ECMO received a palliative care consult. All sites had a dedicated palliative care service. The frequency of palliative care consultation varied by site; at the lowest utilization site, 6% infants who died or were transferred to hospice received a palliative care consult, when compared with 100% at the highest utilization site.

Discussion

Characterizing how infants die is critical to interpreting the impact of illness or interventions in neonatal care.[12] In this cohort, the overwhelming majority of neonates with seizures died after decisions to withhold or withdraw life-sustaining treatment. The most common mode of death, representing nearly half of the infant deaths in this cohort, was death in a *stable* infant who died after a decision to extubate. These results highlight that mortality rates in neonates with seizures are likely driven by treatment decisions about the initiation or withdrawal of life-sustaining therapies. Clinicians must be prepared to help parents caring for infants with seizures understand and process information about neurological prognosis, future quality of life, and complex decision-making.

Death occurred in a variety of circumstances. Most neonates who did not survive died in-hospital, and approximately one-third of infants died during their first postnatal week. A minority of infants were transferred to hospice; some of these children ultimately survived. Unexpected survival after neonatal brain injury has been described previously[13] and underscores the importance of ensuring that families have longitudinal follow-up with health care team members beyond the neonatal period. Pediatric neurologists are well equipped to help families process an unexpected outcome and to manage ongoing neurological symptoms.

High seizure burden (defined as status epilepticus, frequent recurrent seizures without status epilepticus, or many [≥7] isolated seizures) was associated with four-fold increased odds of death or transfer to hospice. A seizure etiology of ischemic stroke was associated with decreased odds of death or transfer to hospice. We hypothesize that these relationships are related to the severity of the underlying brain injury. These findings highlight that neurologists are highly likely to be involved in these complex patients and should be prepared to support families and other clinicians as they make decisions about the provision or discontinuation of life-sustaining treatment.

Families and clinicians received support from a palliative care team in a minority of patients, despite the availability of such services at all participating study centers. Palliative care consultation was more common for infants who died after a decision to either withhold CPR or to extubate in the setting of physiologic stability. This finding highlights the complexity associated with these clinical scenarios, which can require additional decision-making and communication support.[14] Utilization of palliative care consultation and hospice varied by site, likely reflecting the varied availability of services and local culture.[15]

A small number of infants died after a decision to withhold or withdraw artificial hydration and/or nutrition; all three of these infants were from a single institution and were transferred to hospice. Withholding or withdrawing artificial nutrition and hydration in the newborn period is controversial.[16-19] Professional guidelines suggest that this practice is acceptable in select circumstances, including instances in which the child “permanently lacks awareness and the ability to interact with the environment” and when the provision of fluids and nutrition serves solely to “prolong and add morbidity to the process of dying.”[20] The complexity of prognostication required to make these determinations underscores the importance of close coordination between multidisciplinary clinicians, including pediatric neurologists, neonatologists, and palliative care specialists.

This study is strengthened by the large, multicenter, consecutive cohort design, but it is not without limitations. We lack information regarding brain injury severity, for example, neuroimaging, electroencephalography background patterns, seizure semiology, autopsy data, and degree of intracranial hemorrhage, which may influence parent and clinician decision-making. We also do not have access to comprehensive socioeconomic and demographic variables, including insurance status and income, which have been shown to be related to mode of death in the HIE population.[21] Maternal, placental, and intrapartum factors may influence infant mortality and are not fully assessed in this dataset.[22,23] This study

uses information regarding circumstances around the time of death as a proxy for real-time decision-making. The definition of physiologic stability, also used in previous studies,[6,11] does not include indicators of neurological stability, which may inform immediate mortality risk. Future studies should prospectively evaluate the complex decisions that occur between parents and clinicians and the conversations that precede them.

Decisions to withhold or withdraw life-sustaining treatment are common for neonates with seizures and occur throughout the hospital course in varied circumstances. Neurologists caring for infants with seizures must be prepared to partner with families as they make these challenging decisions. Rates of infant mortality in neonatal seizures are influenced by parent-clinician decision-making; how these decisions occur may vary between settings. Future work should characterize how end-of-life decisions occur and how to best support families and clinicians caring for newborns with seizures.

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