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Outcomes after acute symptomatic seizures in neonates

Hannah C. Glass [a, b, *], Zachary M. Grinspan [c], Renée A. Shellhaas [d]

[a] Department of Neurology, Department of Pediatrics, UCSF Benioff Children's Hospital, University of California, San Francisco, CA, USA
[b] Department of Epidemiology and Biostatistics, University of California, San Francisco, CA, USA
[c] Department of Healthcare Policy, Department of Research and Pediatrics, Weill Cornell Medicine, New York, NY, USA
[d] Department of Pediatrics, Department of Communicable Diseases, University of Michigan, Ann Arbor, MI, USA

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A B S T R A C T

Acute symptomatic seizures are a common sign of neurological dysfunction and brain injury in neonates and occur in approximately one to three per 1000 live births. Seizures in neonates are usually a sign of underlying brain injury and, as such, are commonly associated with adverse outcomes. Neurological morbidities in survivors often co-occur; epilepsy, cerebral palsy, and intellectual disability often occur together in the most severely affected children. Risk factors for adverse outcome include prematurity, low Apgar scores, low pH on the first day of life, seizure onset <24 or >72 h after birth, abnormal neonatal neurological examination, abnormal neonatal electroencephalographic background, status epilepticus, and presence and pattern of brain injury (particularly deep gray or brainstem injury). Despite this list of potential indicators, accurate prediction of outcome in a given child remains challenging. There is great need for long-term, multicenter studies to examine risk factors for, and pathogenesis of, adverse outcomes following acute symptomatic seizures in neonates.

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1. Introduction

Acute symptomatic seizures are a common sign of neurological dysfunction in neonates. Despite improvements in neonatal critical care, the estimated rate of seizures in term neonates has not changed considerably in the past two decades and remains approximately one to three per 1000 live births [1,2]. In more than 80% of neonates with seizures, the etiology is an acute symptomatic cause (e.g., hypoxic–ischemic encephalopathy, stroke, hemorrhage) [3]. Seizures may also be the presentation of neonatal epilepsy, which is discussed elsewhere in this issue (Cornet et al. Axeen and Olson). It is, therefore, not surprising that children with a history of seizures in the neonatal period have an associated high risk of death or adverse neurological outcome (including cerebral palsy, epilepsy, global developmental delay, and/or intellectual disability in 35–89%) [4–15]. Neurological morbidities in survivors often co-occur, especially in the most severely affected children [12,13].

The relationship between acute symptomatic seizures and outcomes is not fully resolved. For some newborns, seizures may be only a marker for underlying brain injury [16]. Indeed, some children with a history of neonatal seizures have a good neurodevelopmental outcome [17,18]. However, there is also a body of pre-clinical and clinical evidence suggesting that the seizures themselves are detrimental to the developing brain [6,19,20].

In this article, we review the risk factors for death and disability after acute symptomatic seizures in neonates. We also highlight emerging work to develop clinically meaningful statistical models to predict adverse neurodevelopmental outcomes after neonatal seizures.

2. Mortality

Newborns with seizures have a high risk of death in the neonatal period, ranging from approximately 10%–35% [21]. In a contemporary cohort representing seven US tertiary care centers (Neonatal Seizure Registry), the neonatal mortality rate was 17% [3]. The reasons for the wide variability in reported mortality are unknown, but may be due to differences in referral patterns, different study designs, or variations in practices regarding end-of-life decision-making for neonates with poor neurological prognosis.

Risk factors for death among neonates with seizures are similar to those in all neonates, such as prematurity and severity of illness.

* Corresponding author. University of California San Francisco, Department of Neurology, Department of Pediatrics, 675 Nelson Rising Lane, Room 494, Box 0663, San Francisco, CA, 94158, USA.
E-mail address: Hannah.Glass@ucsf.edu (H.C. Glass).

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Among neonates in the Neonatal Seizure Registry, for example, mortality in the neonatal period (prior to initial hospital discharge) was 39% for extremely preterm infants (<28 weeks), 33% for very preterm (28 to <32 weeks), and 33% for moderate/late preterm infants (32 to <37 weeks), compared with 15% for term neonates ($P < 0.0005$ for preterm versus term mortality) [22]. Similarly, infants with severe underlying neurological injuries, such as intracranial hemorrhage and severe hypoxic–ischemic injury, also have a high risk for early death [21,23]. For survivors, risk of death remains elevated throughout childhood, especially for children with the most profound sequelae, such as severe motor impairment or technology dependence (i.e. tracheostomy or feeding tube) [24].

3. The effects of seizures on the developing brain

Several animal models have been developed to examine the effect of seizures on the developing brain. In some models, seizures induce changes detectable on pathological examination. For example, hippocampal sclerosis may occur in animals that have seizures after an induced brain injury, such as a hypoxic–ischemic insult [25]. However, there are other models in which the hippocampus appears histologically intact, yet alterations in neuronal circuitry impair learning and memory and predispose the animals to subsequent development of epilepsy (see Katsarou et al. in this issue). The mechanisms that underlie seizure-related changes in early brain development vary. These include decreased neurogenesis, delayed neuronal loss, decreased dendritic spine density in hippocampal pyramidal neurons. Changes in hippocampal plasticity have also been described, for example reduced capacity for long-term potentiation, decreased susceptibility to kindling, and enhanced paired-pulse inhibition [26–29].

In humans, it has been harder to untangle the independent effect of seizures on neurodevelopmental outcomes. One possibility is that seizures are an epiphenomenon – i.e., seizures are only a marker of the severity of brain injury, and do not themselves cause additional insult. A second possibility, however, is that seizures are an effect modifier – i.e., seizures augment the damage due to the initial brain injury and thereby lead to worse outcomes. This is an important distinction, because the first possibility (epiphenomenon) suggests that seizures may not require treatment, whereas the second possibility (effect modifier) suggests that seizures should be aggressively treated and, if possible, prevented entirely.

The preponderance of the evidence points to seizures as an effect modifier [6,17,20,30]. The strongest evidence implicating a causal effect of seizures on neurodevelopmental outcomes comes from studies that find a dose–response relationship between seizure burden and outcomes, as highlighted in the following three reports. First, in a recent cohort study of 47 neonates with seizures, a high burden of seizures (>40 min total or maximum hourly seizure burden >13 min/h) increased the odds of adverse outcome (defined as death or significant disability by age 24 months) by more than eight-fold [18]. Interestingly, however, the mere presence or absence of seizures was not associated with outcomes. Second, in an international cohort of children with arterial ischemic stroke that included 28 neonates and 86 children, a longer duration of acute seizures was associated with a higher risk of epilepsy by one year after the stroke [31]. In this cohort, both seizure duration and absolute number of acute symptomatic seizures increased the risk of epilepsy; each 10 min increase in seizure burden was associated with a five-fold increased risk of epilepsy, while children with >10 individual seizures had a 30-fold increased risk of epilepsy compared with those who had no acute symptomatic seizures. Third, in a cohort of neonates with hypoxic–ischemic encephalopathy (HIE), seizure severity was associated with impaired brain metabolism (elevated ratio of lactate to N-acetylcholine on magnetic resonance spectroscopy) and adverse outcome independent of the underlying brain injury [20,32]. In that cohort, children with severe seizures as neonates also had standardized test scores that were two standard deviations below the mean, whereas those with milder seizures had scores that were one standard deviation below the mean [20]. These results persisted even after adjusting for the degree of underlying brain injury.

Not all studies have found a direct effect of seizures on neurodevelopmental outcomes. In a post-hoc analysis of 208 infants with HIE, clinical seizures did not significantly affect the likelihood that an infant would have a low Bayley Scales of Infant and Toddler Development, 2nd edition, Mental Developmental Index, after adjusting for severity of encephalopathy and hypothermia therapy [33]. There were important limitations to this study, however. First, the analysis may have been insufficiently powered to detect a clinically meaningful effect – the point estimate of the effect size was large with a wide confidence interval (adjusted odds ratio: 1.93; 95% CI: 0.83–4.48). Second, the diagnosis of seizures was determined by clinical observation (which is unreliable [34]), without electroencephalography (EEG).

Given the strength of the evidence favoring the idea that seizures add insult to existing brain injury, current clinical practice is to treat neonatal seizures aggressively (see Soul in this issue) [35]. Additional studies are needed to determine whether seizure prevention and aggressive treatment can improve outcomes.

4. Adverse neurodevelopmental outcome

Epilepsy, cerebral palsy, developmental delay and intellectual disability are well-known sequelae of neonatal brain injury (Fig. 1). This is also true in the subpopulation of neonates with acute symptomatic seizures.

4.1. Epilepsy

Epilepsy is a common outcome among neonates with seizures, occurring in approximately 25%. For neonates with symptomatic neonatal seizures, the onset of epilepsy often occurs after a latent period. The acute seizures typically subside within approximately 72 h, and then unprovoked seizures recur after a period of months to years. In most studies, the first year of life is the highest risk period for emergence of post-neonatal epilepsy [36,37]. The high rate of epilepsy onset within the first year may be due in part to a relatively high risk of infantile spasms (approximately 10%), especially among children with severe brain injuries [38]. The risk of epilepsy persists throughout childhood, with some reports of epilepsy onset as long as 15 years after the initial injury [39,40].

Both the brain injury and the presence of neonatal seizures

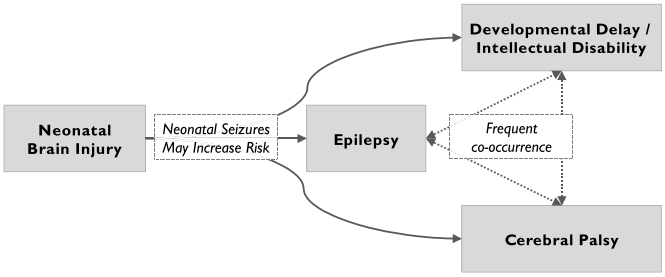

Fig. 1. Epilepsy, cerebral palsy, developmental delay and intellectual disability are sequelae of neonatal brain injury that often co-occur. Investigators have hypothesized that seizures increase the risk of these adverse outcomes. Future studies should target this question to determine whether prevention of seizures, or aggressive treatment when they occur, can improve outcomes.

appear to affect the risk of epilepsy. In one cohort of children with neonatal encephalopathy, all of the children who developed epilepsy had both brain injury apparent on neonatal magnetic resonance imaging and seizures detected in the neonatal period [36]. Children with cerebral palsy also appear to be at higher risk of epilepsy [9,41].

Several studies have examined neonatal risk factors for epilepsy (thoroughly reviewed in 2013 [21] with multiple subsequent studies [13,38,42,43]). Clinical neonatal risk factors include the following: more than one medicine to control neonatal seizures, degree of neonatal encephalopathy, seizure semiology other than focal clonic, abnormal neuroimaging, low birth weight, and low blood pH on the first day of life. Electrographic risk factors for epilepsy include status epilepticus, persistently abnormal EEG background, multifocal (versus focal) seizures, and seizure spread to the contralateral hemisphere.

4.2. Cerebral palsy

Cerebral palsy is also more common among survivors of neonatal seizures than the population at large and has been reported at approximately 15–25% in population-based studies and 30% in the tertiary care setting [44]. The predominant reported cerebral palsy subtype is spastic quadriparesis [45]. Most children with severe cerebral palsy also have a history of global developmental delay [12]. For survivors of neonatal seizures who have cerebral palsy, the odds of co-morbid post-neonatal epilepsy increase eight-fold [46]. Conversely, most of those with post-neonatal epilepsy also have cerebral palsy [9,41].

4.3. Global developmental delay and intellectual disability

Global developmental delay was reported in about 40% of children who survived neonatal seizures at a single center. Many of these children were later diagnosed with intellectual disability or cerebral palsy [45]. In a population-based study of outcomes of neonates with clinically diagnosed seizures, 20% had intellectual disability and an additional 27% had learning disorders [9].

5. Limitations of current research

Whereas neonates with seizures are known to be at higher risk for adverse neurodevelopmental outcomes including developmental delay, intellectual disability, cerebral palsy, and epilepsy, determining the precise risk remains a challenge for several reasons. First, diagnosis of seizure may be based on clinical events without continuous video-EEG monitoring (or with only brief monitoring), making assessment of the presence and severity of seizures inaccurate. Without reference standard EEG diagnosis, seizures may be over-reported, as many clinical events noted at the bedside are not true epileptic seizures [34,47], or under-reported, as electrographic seizures are often clinically silent [3]. Second, most cohort studies include children with heterogeneous etiologies and neuropathologies for seizures with known differences in expected outcomes (e.g. children with neonatal onset epilepsies, acute symptomatic seizures, and children with transient causes of seizures have predictably divergent expected outcomes). Third, patient selection is variable by study, and some populations may be enriched for more severe cases (e.g., those selected from neurology follow-up clinics or tertiary/quaternary care centers). Reported rates of disability are higher among intensive care-based studies as compared to population-based studies [44]. Fourth, standardized testing for large cohorts is challenging as there are no reference standards for definition of impairment, and no agreement on the best timing for follow-up evaluations. The likelihood of participating in follow-up testing may vary by clinical outcomes, distance to the testing center, family satisfaction with care, availability of alternative providers of care, or other reasons – any of these can bias results. As such, many studies rely on a broad classification of "unfavorable" versus "favorable" outcomes, which may be defined in terms of motor impairment (using standardized testing, neurological examination, or validated motor scales such as the Gross Motor Function Classification System), cognitive disability (based on developmental testing), sensory impairment (hearing and vision impairment), epilepsy, or the clinical impression of the treating neurologist. Finally, cognitive and behavioral outcomes can only be assessed with long-term follow-up, which is limited by attrition, short-term grant funding cycles, and cost of developmental assessment.

6. Determining the risk of adverse outcome: prediction models

Despite these limitations, several prediction scoring systems have been developed to identify which children are at high risk to develop adverse neurodevelopmental outcome [15,43,45,48]. Common predictors include delivery by cesarean section, low birth weight, low Apgar scores, low pH on the first day of life, seizure onset <24 or >72 h after birth, abnormal neonatal neurological examination, abnormal neonatal EEG background, status epilepticus, and presence and pattern of brain injury, among others (Table 1).

Although the details of the published approaches to prediction differ, there are several common themes. First, many of the statistical models consider multiple factors, often in multiple domains (clinical, laboratory, EEG, and imaging), and at different lengths of time after birth. This observation highlights that successful prediction of outcome is improved by comprehensive evaluation of brain-injured newborns. Second, the pieces of information incorporated into the statistical models are typically available within the first few days of life, which suggests that the risk of adverse outcomes can be determined with reasonable accuracy early in the clinical course. Third, in at least one study [43], predictions were robust to variations in clinical interpretation of diagnostic tests, which illustrates that poor inter-rater reliability of diagnostic testing and clinical examination may not significantly reduce the accuracy of a statistical model that incorporates information from multiple sources.

Prediction models are important for tailoring parent counseling and frequency of follow-up evaluations, as well as optimizing developmental interventions. Robust prediction models are important to improve models to identify children at both low and high risk for poor outcomes, which will allow clinicians to provide reassurance to parents of some neonates with mild and/or transient neurological dysfunction, despite the presence of seizures.

7. Summary

Seizures in neonates are usually a sign of underlying brain injury and, as such, are commonly associated with adverse outcomes. Depending on the study, adverse outcome is reported to occur anywhere from approximately 30–90%. Small studies have shown that examining clinical risk factors and seizure etiology can help the treating provider estimate the risk of adverse outcome, especially for those with very poor or very good prognosis. Children whose acute symptomatic neonatal seizures are associated with persistently abnormal EEG background or with high seizure burden are at high risk of death or disability. Conversely, neonates with seizures but without other risk factors may be spared severe disability. Epilepsy occurs in approximately 25% of survivors and often co-occurs

Table 1
Risk factors for adverse outcomes after acute symptomatic seizures in neonates.

Risk factor	Low risk	Intermediate risk	High risk
Delivery type [45]	Vaginal	Cesarean	
Birth weight [48]	>2500 g	1000–1499 g 1500–2499 g	<1000 g
Apgar score at 1 min [48]	8–10	4–7	0–3
Seizure onset [45]	Between 24 and 72 h of life	<24 h of life	>72 h of life
Lowest pH on first day of life [43]	>6.8		≤6.8
Neurological examination [48]	Normal or mildly abnormal	Moderately abnormal	Severely abnormal
EEG background [43,45,48,49]	Normal or mildly abnormal	Moderate or severely abnormal	Burst suppression pattern
Antiseizure medication efficacy [48]	Immediate response	Partial response	No response
Neonatal status epilepticus [48]	Absent		Present
Semiology [45]	Focal clonic		Subtle, multifocal clonic, tonic, myoclonic
Seizure etiology [45]	Intracranial hemorrhage or ischemic stroke	Hypoxic–ischemic encephalopathy	Infection
Ultrasound results [48]	Normal	IVH I or II, transient echodensities, mild ventricular dilatation	IVH III, PVHI
Pattern of brain injury [38,42,43]		Cortical injury	Deep gray injury Brainstem injury

EEG, electroencephalography; IVH, intraventricular hemorrhage; PVHI, periventricular hemorrhagic infarction.

with developmental delay or intellectual disability and/or cerebral palsy.

Studies examining outcomes following seizures in neonates must be interpreted with caution since most are single center, use video-EEG for seizure diagnosis inconsistently, have limited duration of follow-up, combine acute symptomatic seizures with early onset epilepsies, or were conducted prior to the widespread use of therapeutic hypothermia for HIE (which appears to decrease the risk of acute neonatal seizures in neonates with moderate encephalopathy) [50–52]. There is great need for long-term, multicenter studies to examine risk factors for, and pathogenesis of, specific adverse outcomes following acute symptomatic seizures in neonates. Such studies should build upon and validate the initial published statistical prediction models derived from smaller cohorts to identify which neonates with seizures are at high (or low) risk for adverse outcomes. Such data will help researchers to design more efficient trials to identify candidates for intervention and will guide clinicians in their care of newborns with seizures.

7.1. Practice points

- Risk factors for death and disability after acute symptomatic neonatal seizures include preterm birth, persistent severely abnormal EEG, and injury to the deep gray nuclei and brainstem on MRI.
- Epilepsy, cerebral palsy, developmental delay and intellectual disability are sequelae of neonatal seizures that often co-occur.

7.2. Research directions

- The role of seizure prevention and acute treatment to improve outcomes after acute symptomatic neonatal seizures.
- The role of novel agents to prevent epilepsy after brain injury and neonatal seizures.
- The mechanisms of epileptogenesis after neonatal seizures.
- Long-term and multicenter studies to develop accurate risk models to predict adverse outcomes.

Conflict of interest statement

None declared.

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