Seminars in Fetal & Neonatal Medicine xxx (2018) 1–5

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Outcomes after acute symptomatic seizures in neonates

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Keywords:
Neonatal seizures
Electroencephalogram
Epilepsy
Neonatal encephalopathy
Hypoxic–ischemic encephalopathy
Cerebral palsy
Intellectual disability

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.

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.

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https://doi.org/10.1016/j.siny.2018.02.001
1744-165X/

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

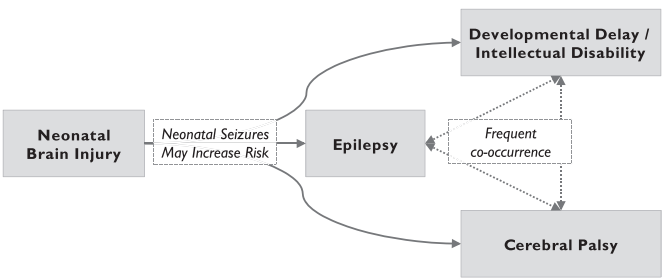

Fig. 1. Epilepsy, cerebral palsy, developmental delay and intellectual disability are sequelae of neonatal brain injury that often co-occur. Investigators have hypothesized that seizures increase the risk of these adverse outcomes. Future studies should target this question to determine whether prevention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

Please cite this article in press as: Glass HC, et al., Outcomes after acute symptomatic seizures in neonates, Seminars in Fetal & Neonatal Medicine (2018), https://doi.org/10.1016/j.siny.2018.02.001