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Outcome following neonatal seizures

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SUMMARY

Neonatal seizures are the most common manifestation of neurological disorders in the newborn period and an important determinant of outcome. Overall, for babies born at full term, mortality following seizures has improved in the last decade, typical current mortality rates being 10% (range: 7–16%), down from 33% in reports from the 1990s. By contrast, the prevalence of adverse neurodevelopmental sequelae remains relatively stable, typically 46% (range: 27–55%). The strongest predictors of outcome are the underlying cause, together with the background electroencephalographic activity. In preterm babies, for whom the outlook tends to be worse as background mortality and disability are high, seizures are frequently associated with serious underlying brain injury and therefore subsequent impairments. When attempting to define the prognosis for a baby with neonatal seizures, we propose a pathway involving history, examination, and careful consideration of all available results (ideally including brain magnetic resonance imaging) and the response to treatment before synthesizing the best estimate of risk to be conveyed to the family.

1. Introduction

Seizures are the most frequent manifestation of neurological disorders in the newborn period. The reported prevalence varies widely, depending on the baseline population and the diagnostic criteria used. Most outcome data come from case series in which the diagnosis was purely clinical. Clinical diagnosis of seizures generally underestimates the electrical seizure frequency, and the first reported clinical seizure is also an unreliable time point.[1] There are no large studies of outcome following prospective electroencephalographic (EEG) monitoring.

The estimated prevalence of babies with clinical seizures is around 1–3 per 1000 live births. In the preterm population this is even higher and seizures are more prevalent at lower gestational ages and lower birthweight. Reports describe rates of 2–3 per 1000 live births in general population and term babies; 4.4 per 1000 live births between 1500 and 2500 g; 55–130 per 1000 live births <1500 g and up to 64 per 1000 live births in infants <1000 g birthweight.[2–10] Most of the studies reporting the prevalence of seizures in preterm babies are from an era when intraventricular haemorrhage (IVH) was far more common than currently. Recently, West et al.[11] used amplitude-integrated (a)EEG monitoring prospectively in a cohort of 84 babies born before 29 weeks of gestation and admitted to their unit in Auckland in 2002–2004, none of whom was considered to have clinical seizures: five had definite electrographic seizures (four of whom died and the other survived with multiple disabilities).

Although the prognosis for term and particularly preterm babies has generally improved in the last decades, seizures still identify those babies at increased risk of dying or surviving with neurological impairment, developmental delay or later epilepsy. The rate of unfavourable outcome is higher when there is EEG confirmation.[11–14] The main predictor of adverse outcome remains the underlying cause, particularly global hypoxic–ischaemic injury. The debate as to whether the seizures themselves – or non-treatment of seizures – can cause additional brain injury and contribute to later impairment is still unclear. Certainly the presence of continuous or very frequent seizures (status epilepticus) may lead to neuronal damage in the experimental model.[2,15,16] One human neonatal trial of treatment to electrical quiescence using aEEG monitoring showed an association between the seizure burden and severity of brain injury measured with magnetic resonance imaging (MRI), but these results await confirmation.[14]

In our opinion the clinician should only attempt to give a prognosis to the parents of a baby with seizures after consideration of all the available information. Current standards of investigation should enable the cause to be determined in the vast majority of

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cases. With routine ultrasound imaging only 5 of 61 (8%) babies in Leeds were considered to have seizures of unknown cause, and a similar percentage of 'unknown' cases was reported in 2002–2007.[17,18] The prognosis can then be refined according to the underlying cause, the duration of seizures and the response to treatment, and may include information from serial examination of the baby and the results of investigations including neuroimaging and the background EEG (Fig. 1).

2. Mortality

In term babies, mortality following seizures has fallen from 40% before 1969 to around 7–16% in more recent reports (Table 1), but overall rates of impairment remain at around 30% (Table 2).[19] Mortality is higher in preterm babies with seizures, ranging from 22% to 58% (Table 3). In term babies, those with inborn errors of metabolism or severe hypoxic–ischaemic encephalopathy (HIE) have the highest mortality, although therapeutic hypothermia has altered the pattern of outcome following HIE, reducing the risk of death. Twenty-three of 77 admissions (29%) to the Connecticut neonatal intensive care unit (NICU) between 1992 and 1998 died during their stay on the unit.[20] In our own experience, during the 42 months between 2009 and 2012, 63 babies were admitted with EEG confirmation of seizure, of whom 13 (20.6%) died; 9/50 were term and 4/13 were preterm. Our institution is a referral centre for therapeutic hypothermia: 67% of deaths in the term group were due to severe HIE, and all babies died after withdrawal of care because of a poor prognosis, which may explain our relatively high mortality.

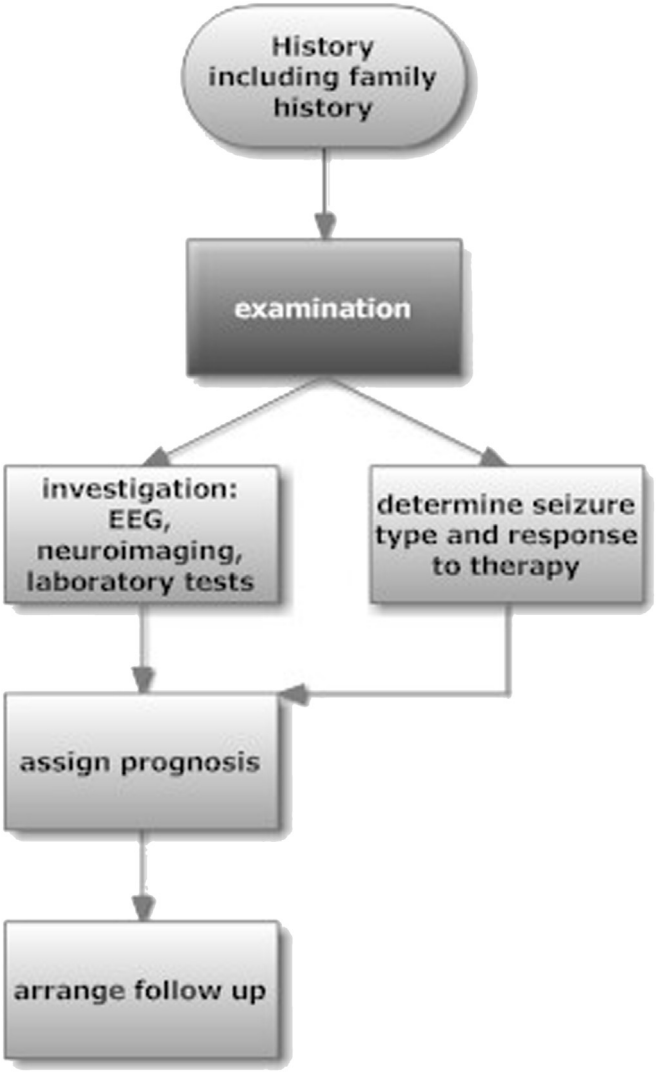

Fig. 1. Pathway for estimating the risk of adverse outcome in neonatal seizures.

3. Adverse neurodevelopmental outcomes

3.1. Experimental evidence

There is a considerable body of evidence from experimental data showing that neonatal seizures can adversely affect the developing brain.[15] Brain development may be altered even after brief seizures. Brain injury following repetitive seizures may occur via several mechanisms, such as hypercapnia, hypoxia, alteration in cerebral blood flow (producing ischaemia or haemorrhage), decrease in energy substrate (brain glucose), increase in lactate, or through release of excitatory amino acids.[3,15] Recurrent seizures, individually not necessarily prolonged, are associated experimentally with long-term functional, morphological and physiological deficits in animal models.[15] The main abnormalities observed are in synaptogenesis (rather than neuronal loss), and the hippocampus appears to be most sensitive in terms of neurogenesis and synaptic reorganisation.[21] Synaptic reorganisation, manifest as mossy fibre sprouting, is seen in the dentate granule cells of the hippocampus of immature rats who have seizures induced with flurothyl.[21]

For a more detailed review on the mechanisms of neonatal seizures, see Y. Ben-Ari, 'Mechanisms and effect of seizure in the immature brain' of this issue.

3.2. Clinical evidence

Glass et al. evaluated 143 infants with HIE, 32% of whom had clinically identified seizures.[22] The presence of seizures was associated with adverse long-term outcomes at 4 years of age, the prevalence of which was higher with increasing severity of seizures. This association was independent of the severity of HIE or brain injury. Using multivariate regression analysis to examine the effect of seizures on outcomes, and controlling for the severity of HIE using an MRI score to document brain injury, infants who had severe neonatal seizures had global intelligence quotients which were substantially lower than those with fewer seizures. Children with mild–moderate seizures had intermediate outcomes. Thus it seems likely that the presence and frequency of seizures indicates either a more serious injury or may cause independent neurological damage that leads to later impairment.

Babies that present with very frequent recurrent seizures or neonatal status epilepticus generally have a very poor outcome – in one study of 56 neonates with status epilepticus this was as high as 75%.[16] In another study of neonatal seizures, status epilepticus persisting for more than 30 min was associated with death or impairment in 90%.[12]

3.3. EEG evidence and the influence of background EEG on prognosis

Certain electrographic seizure characteristics correlate with an unfavourable prognosis.[2,12,13,23,24] For example, some studies have associated poor neurological outcome with higher seizure frequency (>5/h) and babies with HIE who have a high seizure burden have a worse outcome.[13,25] These findings are consistent with previous reports that a longer duration of electrical seizures is