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Status epilepticus in the neonate

Lakshmi Nagarajan ,[1,2] Soumya Ghosh[1,3]

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[1]Neurology, Perth Children's Hospital, NEDLANDS, Western Australia, Australia
[2]Paediatrics, University of Western Australia, NEDLANDS, Western Australia, Australia
[3]Perron Institute for Neurological and Translational Science, University of Western Australia, Nedlands, Western Australia, Australia

Correspondence to
Prof Lakshmi Nagarajan; lakshmi.nagarajan@health.wa.gov.au

ABSTRACT

Status epilepticus in the neonate (NSE) is a medical emergency that often results in dire consequences. Minimising injury from NSE is essential. The diagnosis of NSE can be challenging as neonates frequently have electrographic only seizures and an EEG is essential for recognition of seizures and seizure burden. The lack of a universally accepted definition of NSE, possible adverse effects from commonly used antiseizure medications, debate regarding the best treatment packages for NSE, limited access to EEG and investigations for aetiology of NSE add to the clinical conundrum. In this review, we aim to present what is known, highlight the importance of EEG monitoring for diagnosis and treatment, discuss what is not known and suggest a practical paradigm for the management of NSE.

KEY MESSAGES

⇒ Neonatal status epilepticus is a neurological emergency and is associated with significant morbidity and mortality.
⇒ Diagnosis of neonatal status epilepticus is challenging due to lack of a universally accepted definition and the need for EEG monitoring to accurately identify and quantify neonatal seizures.
⇒ Aetiology of neonatal status epilepticus includes a wide spectrum of disorders, some of which may not be identified early.
⇒ Treatment for neonatal status epilepticus must be timely and individualised to optimise efficacy of interventions and minimise adverse outcomes.
⇒ Harnessing advances through computer learning and artificial intelligence may facilitate early diagnosis, prognostication and better outcomes for infants with neonatal status epilepticus.

STATUS EPILEPTICUS IN THE NEONATE

It is universally agreed that the outcome of babies with status epilepticus (SE) in the neonatal period (NSE) is not good, with unacceptable mortality and morbidity.[1–4] The diagnosis and treatment of NSE are a challenge as there is no single definition of SE in the newborn and no ideal antiseizure medication (ASM) for treatment. Treatment pathways are variable. We need to consider the detrimental effects of seizures on the immature brain and its development, as well as the possible adverse effects of ASMs and neuroprotective strategies employed. In this review, we aim to highlight what is known, discuss what is unknown and suggest a practical paradigm for the diagnosis and appropriate treatment of NSE. Treatment of NSE should ideally begin with early detection and treatment of neonatal seizures (NS), identification of risk factors for NSE and treatment escalation as seizures continue or progress.

DEFINITION

There is significant variation in the definition of NSE across the world. Recent guidelines from the International League Against Epilepsy (ILAE) task force on classification of seizures and epilepsies in the neonate[5 6] and treatment of seizures in the neonate[7] do not specifically address the question of what qualifies as NSE and how to manage it. A scoping review[8] from the ILAE neonatal task force demonstrated a substantial variation in definition of NSE across the literature. The authors propose a neonatal task force to develop a standardised approach to assessing and describing seizure burden and defining NSE.

The ILAE task force on classification of status epilepticus[9] proposed a new conceptual definition with two operational dimensions of time points: t1 indicating when treatment should be initiated and t2 when long-term consequences may appear. Both these time points are based mostly on animal and clinical research of convulsive status epilepticus and provide a basis to find a safe and practical guideline for clinical purposes. t1 and t2 vary by seizure type in this definition. We know that in neonates with seizures, longer seizure durations and greater seizure burden/ictal fraction are associated with lesser response to ASMS, longer hospital stays and adverse neurological consequences.[10–12] With current knowledge, it is not possible to nominate a t1 and t2 for NSE and this classification with its four axes[13] may not be appropriate for NSE.

Lack of an accepted definition of a neonatal seizure and NSE creates uncertainty, and a consensus is essential for clinical care guidelines and protocols, epidemiological and clinical research studies, as well as for artificial intelligence (AI) and automated seizure

prediction and detection algorithms.[14–16] Due to the lack of clear guidelines, continued use of the conventional definition of NSE as continuous seizure activity for at least 30 minutes or recurrent seizures for 50% or more of a 1 hour epoch seems sensible.[17–20]

DIAGNOSIS

Continuous Video-EEG (cVEEG) monitoring is essential for the detection and diagnosis of NSE, to tailor treatments, assess response to interventions and for prognostication.[21–23] Neonates may have electrographic only seizures (ESZ only), electroclinical seizures (ECSZs) or a mixture of both.[6 24–28] cVEEG allows accurate estimation of seizure frequency, duration of individual seizures, type of seizure, seizure onset and propagation patterns, as well as the overall seizure burden (defined as the number of electrographic seizure seconds in the total EEG recording or the accumulated duration of EEG seizure activity over a defined period of time)[21 22 29]: these features are considered to have prognostic implication.[24–26 29–32] Figure 1A illustrates some features of neonatal seizures in a preterm infant with severe hypoxic ischaemic encephalopathy (HIE). Figure 1B shows a focal ictal discharge that migrates from one hemisphere to another, within the same seizure, in a term infant with a genetic developmental and epileptic encephalopathy (DEE) and an early-onset epilepsy of infancy with migrating focal seizures. Amplitude-integrated electroencephalography (aEEG) may be used for diagnosis of NSE, with cognisance of its limitations, when full conventional EEG (the accepted gold standard for EEG monitoring) is not available.[3 6 16 23 33 34] Machine learning, AI, quantitative electroencephalography and automated seizure detection programmes are being used increasingly to facilitate easy, early interpretation of the EEG data and prompt treatment. Deep learning models for neonatal seizure detection promote working of human and artificial intelligence synergistically and have the potential to improve outcomes globally in neonates with seizures and NSE.[35]

The current ILAE classification of seizures in the neonate[6] emphasises the role of the EEG for diagnosis of NS. It does not require the 10 s duration rule for diagnosis of an EEG seizure. This allows inclusion of brief ECSZs such as myoclonic seizures and epileptic spasms. It has been proposed that brief EEG rhythmic discharges (BERDS, BRDs) of <10 s duration are mini seizures, with prognostic implication[32 36]. The ILAE paper[6] suggests that BRDs in neonates may be part of the ictal-interictal continuum. The question of whether BERDS/BRDS should be included in the seizure burden remains open and worthy of further study.

The EEG signature of seizures in neonates may be unique and difficult to recognise, requiring expertise in interpretation (figure 1).[21 25 26 37] Combining clinical, VEEG, neuroimaging and genetic information may allow distinction between acute provoked seizures and the neonatal-onset epilepsies and identify aetiology-specific electroclinical syndromes (figure 1B), thus enabling more targeted interventions.[16 38–40]

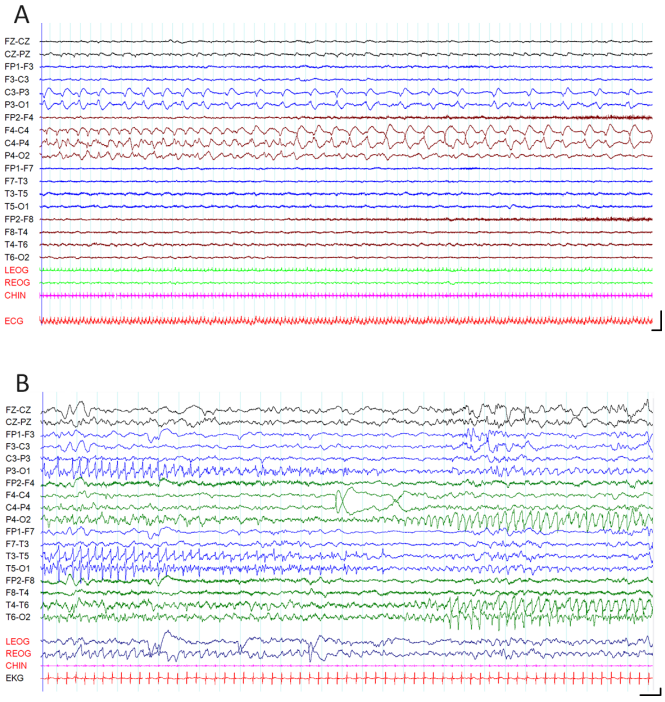

Figure 1 EEG in neonatal status epilepticus. A. Preterm neonate born at 34^{+4} weeks gestational age with severe HIE and electrographic only status epilepticus. EEG on day 1 (1 min epoch) shows prolonged multifocal seizures from both hemispheres. Ictal EEG shows rhythmic slow sharp discharge on the left (frequency <1/s) and faster rhythmic discharge on the right. There is a smaller amplitude discharge from the midline. Background is abnormal (low amplitude). ECG artefact seen in EOG and Chin EMG. Montage is longitudinal bipolar (double banana)—left-sided derivations in blue, right-sided in red, midline in black. Calibration bars for EEG (bottom right): vertical 100 µV horizontal 1 s. B. Term neonate with genetic DEE, epilepsy of infancy with migrating focal seizures and in status epilepticus. Ictal EEG (30 s epoch) shows seizure discharge migrating from the left occipito-temporal region hemisphere to the right occipito-temporal region. Montage is longitudinal bipolar (double banana)—left-sided derivations in blue, right-sided in green, midline in black. Calibration bars for EEG (bottom right): vertical 100 µV horizontal 1 s. Bipolar lead abbreviations based on international 10–20 system; DEE, developmental and epileptic encephalopathy; EEG, electroencephalogram; EMG, electromyogram; EOG, electrooculogram; HIE, hypoxic ischaemic encephalopathy.

AETIOLOGY AND PATHOPHYSIOLOGY

NSE is estimated to occur in 15%–25% of babies with seizures. Acute symptomatic or provoked seizures due to HIE, strokes, intracerebral haemorrhage and infections are responsible for about 75% of NS and NSE.[1 20 41–43] Genetic epilepsies, for example, those related to ion channel dysfunction, vitamin-dependent

disorders, metabolic disorders and structural brain abnormalities (genetic or due to antenatal brain injury) result in unprovoked seizures in about 15%–20% of babies with NS.[5 44 45] NSE can occur in both the provoked and unprovoked seizure categories, more often in symptomatic/provoked seizures.[20] EEGs and MRI brain may provide clues to the aetiology and extent of brain injury and often particularly useful in prognostication.[46–48] Seizures in the neonate occur more frequently than in any other period in life and NS evolve to NSE in 8%–43%. HIE is often the most frequent aetiology for NSE. A study[49] comparing characteristics of neonates with NSE with those who had NS (but not NSE) showed that hypoglycaemia in the first few hours of life and a severely abnormal initial neurological examination were found to be predictive of NSE. The presence of subclinical seizures, monotherapy treatment failure and distribution of seizure burden (including status epilepticus) has been found to be similar in preterm and term neonates.[1]

The neonatal period is a unique time of brain development with rapid growth, maturation of cortical neurons, and formation of exuberant synapses and connections. The pattern and trajectory of synaptic plasticity, the distribution of neurotransmitters, neurotrophins and peptides, the maturation patterns of cation chloride cotransporters and the developmental regulation of genetic programs result in enhanced excitability and contribute to the vulnerability of the neonatal brain to seizures and seizure-related injury.[48 50] The concept that seizures beget seizures is probably applicable to NSE. The molecular, cellular and network changes that result in NSE and in secondary epileptogenesis are complex and not completely understood.[25 49 51–54] In a review entitled 'In the Fast lane: Receptor trafficking during status epilepticus', Naylor[55] explains how excess seizures trigger a cascade of shifts in receptor subunit composition and surface representation resulting in an imbalance between GABAergic inhibition and glutamatergic excitation in the brain. The resultant intensified excitation and reduced synaptic inhibition sustain seizures and contribute to spontaneous recurrent seizures and cognitive sequelae. Minimising injury from NSE is challenging and is an important focus for continued research.

TREATMENT

The treatment of NS and NSE is part of a continuum. What to treat, when to treat and with what to treat are still debated in the NS and NSE arena. Lack of a universally accepted definition of an EEG seizure and status epilepticus in the neonate, varied classification of neonatal seizures (combinations of clinical only, ESZ only and ECSZs), and uncertainty regarding impact of pretreatment delay have resulted in a wide spectrum of protocols in clinical care and trials.[7 38 56–59] Treatment is also guided by clinical features (seizure frequency, seizure duration), EEG features (background, ictal and interictal discharges) and seizure burden before and after initiation of ASM. There is general agreement that treating all electrographic seizures (ESZs and ECSZs) may be associated with improved outcomes.[7] EEG confirmation of seizures is essential; however, in resource-limited settings, treatment is often based on aEEG or clinical diagnosis only.

The importance of differentiating acute provoked seizures from neonatal-onset epilepsies for optimal management is intuitive. Though management with ASMs is similar initially, it then needs to be tailored for the aetiology.[38 39 44 60] Treatment pathways aim for cessation of NS, trying to prevent NSE and minimise the seizure burden. The importance of good antenatal and neonatal intensive care, practical protocols with capacity to individualise use of ASMs, vitamins, diet, neuroprotective strategies and targeted therapy is well recognised. Involvement of the family in decision making is crucial.

The special report from the ILAE Task Force on Treatment of Neonatal seizures recommends that phenobarbital (PB) should be the first-line ASM. When history and clinical profile point to a channelopathy, phenytoin or carbamazepine may be used[7], and oxcarbazepine and lacosamide may also be considered. A randomised control trial[61] and a Cochrane review[57] on ASMs for seizures in neonates also indicate that phenobarbitone is more effective than levetiracetam as first-line therapy. Addition of bumetanide to PB may be no better than PB alone, though altering cation chloride transport is an option being explored in further studies.[40] The best second-line ASM is still unclear with phenytoin, levetiracetam, midazolam and lignocaine being equivalent choices; levetiracetam may be the preferred option if there are cardiac problems.[7 38 57] A trial of pyridoxine is warranted in neonates with clinical features of B6-dependent epilepsy and seizures that have not responded to second-line drugs.[7 45] Therapeutic hypothermia (TH) may reduce the seizure burden, but it is not known if it will prevent NSE.[38 58] There is uncertainty regarding any benefit and possible harmful effects of TH for neonatal encephalopathy in low-income and middle-income countries.[62 63] The treatment protocols for recurrent seizures in the neonate and neonatal status are similar with escalation of use of ASMs in NSE. Children and adults with refractory SE (seizures despite administration of at least 2 ASMS that are appropriately chosen and dosed) are often treated with anaesthetic agents. Midazolam, considered to be an anaesthetic agent, is frequently used in NS and NSE. Propofol is rarely used in neonates because of the risk of propofol infusion syndrome. Inhalational agents, such as sevoflurane, are also not routinely used for NSE. Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, may have a useful role to play in NSE, despite the limited amount of data in neonates.[64 65] As an N-methyl-D-aspartate receptor antagonist, it may have a specific role in ATP1A2 related and other DEEs associated with excess excitatory neuronal activity.[66] Topiramate, valproate, zonisamide, vigabatrin, lacosamide, perampanel and steroids are additional drugs that are trialled when NSE is refractory.[38] It

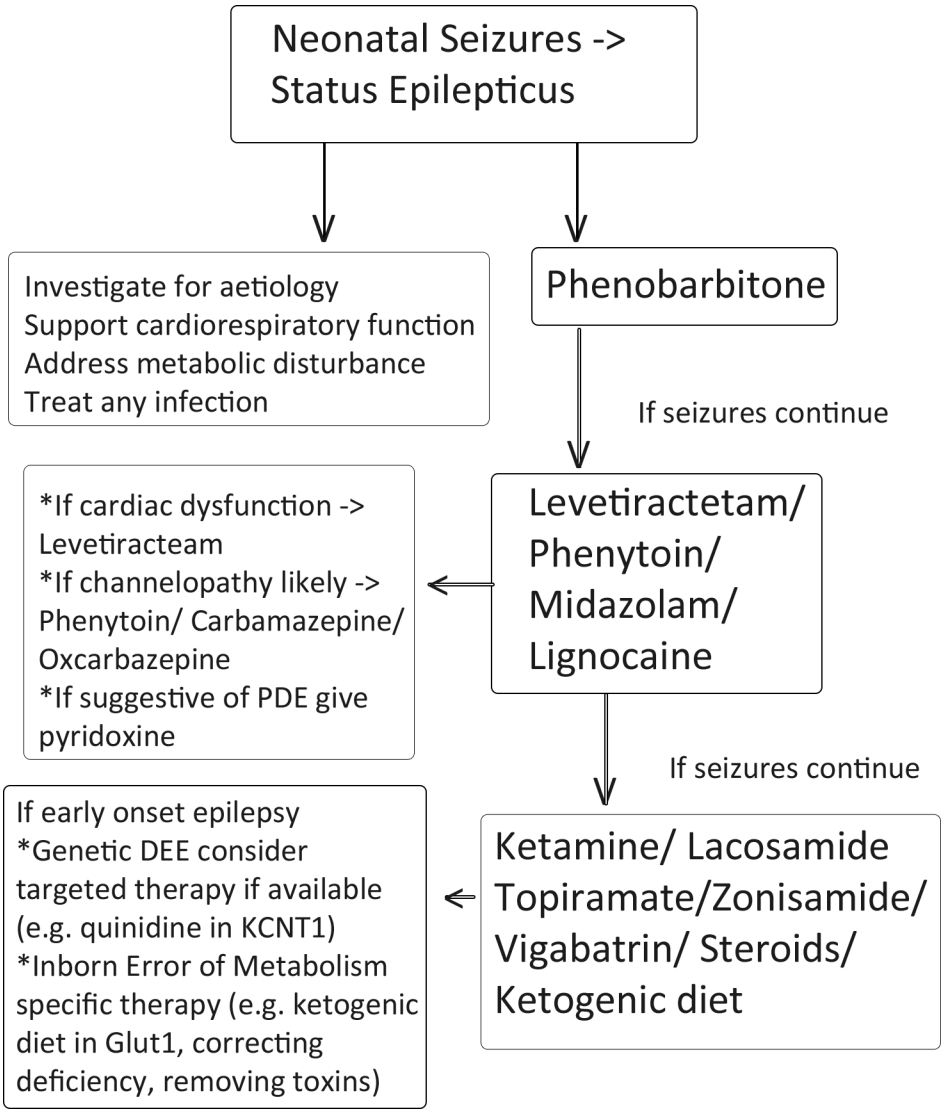

Figure 2 Flow chart for management of seizures and status epilepticus in the neonate. DEE, developmental and epileptic encephalopathy; Glut1, glucose transporter deficiency disorder; KCNT1, potassium sodium-activated channel subfamily T member 1; PDE, pyridoxine-dependent epilepsy. Figure legends: Neonatal status epilepticus.

is essential to have good neonatal intensive care teams to address the multisystem complications and comorbidities associated with NSE.[67]

The flow chart on NSE management (figure 2) provides a practical management pathway for NSE and NS. The initial investigations (in the first 24–48 hours) would include an EEG, neuroimaging (US/MRI) and blood/urine/CSF tests screening for infections, undertaking basic metabolic tests such as glucose, urea, electrolytes, creatine, uric acid, plasma amino acids, ammonia and urine metabolic screen. If NSE is not responsive to two or more ASMS, or seizures continue beyond 48–72 hours, additional tests would be tailored to the individual neonate and may include further exploration of genetic DEEs and inborn errors of metabolism, as well as consideration of therapeutic interventions such as a ketogenic diet. If a genetic diagnosis or a neurometabolic cause is identified, therapy may be targeted to the aetiology, such as removal of toxic metabolites, special diets, vitamin or other supplements, NMDA antagonists, etc.

A positive family history and lack of evidence of a provoked cause for the NS and NSE should result in investigations for a genetic/metabolic cause for the neonatal epilepsy.[5 68–70] Targeted gene panels and next-generation exome and genome sequencing have identified several variants associated with early-onset seizures in self-limiting epilepsies and the DEEs. Disease-modifying therapies, purposefully designed for specific mechanisms and pathways, are available or being developed for some.[40] Epilepsy surgery in young infants may be an effective treatment for NS and NSE.[71 72] However, it is often reserved for those with catastrophic presentations, and counselling and ethics may be challenging.

The ketogenic diet may be efficacious in recurrent seizures and NSE due to genetic and metabolic DEEs.[73–75] It is the treatment of choice for pyruvate carboxylase

dehydrogenase and Glut1 deficiency disorders related to NS/NSE.

Neuroprotective and neurorestorative strategies are based on the concept of brain damage evolving over time and providing a window of opportunity to intervene at specific time points with known and novel therapies.[41 48 49 76] The best protocols for improved long-term outcome need to be determined by multicentre trials investigating combinations of ASMs, individual-specific interventions (eg, pyridoxine in PDE, trial of quinidine in KCNT1 gene-related NSE, sodium channel drugs for channelopathies) and other strategies such as therapeutic hypothermia and neuroprotective pharmacological interventions. Recent developments such as cell therapy and microRNA-based therapies will be included in the multimodality management plan as they become available.[40]

PROGNOSTICATION

Accurate prognostication of outcomes enables appropriate decision making in NSE. In view of the possible severe sequelae from NSE[11 24 49 77], a discussion regarding options and ceilings of care, including initiation of palliative care, may need to be undertaken in critically ill neonates if prognosis is deemed poor. Clinical history and examination, family history, EEG (background, seizure burden, ictal and interictal epileptiform activity and propagation patterns), neuroimaging, metabolic profile (transient aberrations and inborn errors) and any other available information (eg, genetic) must be used.[3 4 11 24–26 30–32 42 47 49 78] Abnormal neurological examination at discharge following NS or NSE and a family history of epilepsy have been reported to be predictive of outcome.[49 79] Specific aetiological or syndromic diagnosis may provide more precise information for prognostication.

OUTCOME

Neuronal injury from NS and NSE often results in long-term neurodevelopmental sequelae such as cognitive and motor disability, learning difficulties, behavioural impairment, sleep dysfunction and epilepsy. It may also result in mortality in the neonatal period and early childhood. Newborns with NSE had a high risk of mortality, with birth weight, severely abnormal neuroimaging and NSE being independent predictors of adverse outcome.[80] Preterm infants with seizures and NSE in the neonatal period continue to have higher risk of abnormal neurodevelopmental outcomes compared with preterm infants without seizures and term infants with seizures.[1 2 81]

A systematic review of outcomes after neonatal seizures (verified by EEG) reported a wide spectrum of abnormalities following NS and NSE[4]: post neonatal epilepsy in 46.1% to 83.3%, cerebral palsy in 67%–100% and mortality of 0%–45% was reported in babies with NSE. Incidence of intellectual disability (23.8%–38.6%) and developmental delay (10%–63%) was reported for NS but not specifically for NSE. An earlier systematic review[78] that included EEG verified and not verified seizures showed a similar spread of outcomes. Selection bias, variable definitions of ESZs and NSE, different follow-up measures and duration, diverse aetiologies and different geographical locations may have contributed to this variability of outcomes. More than 50% of survivors of seizures and NSE in the neonatal period have neurodevelopmental disability of some form.[4 31 77] Seizure burden is related to worse outcomes, with neurological dysfunction and mortality being highest in NSE.[4 12 42 49] Future population-based, multicentre studies of outcome measures, with standardised definitions of NS and NSE, are needed.

FUTURE CHALLENGES IN NSE

We lack a clear understanding of the best operational definition of NSE, when to initiate ASMs, which ASMs to use and in what order (to optimise outcomes and minimise long-term sequelae), and how to best prognosticate immediate and long-term outcomes. While a lot of literature is available regarding NSE, there is a need for strategically designed large multicentre studies, inclusive of a variety of socioeconomic and geographic locations, incorporating treatment bundles designed for specific aetiologies and gestational ages, and standardised assessment of outcomes over childhood and adolescence. NSE is a neurological emergency that often results in dire consequences. The Intersectoral Global action plan[82] may provide a unique opportunity for international epilepsy, child neurology, neonatal and paediatric associations to work together to raise awareness of NSE, promote education and research, as well as advocate for resources to optimise brain health in survivors of NSE across the world.

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ORCID iD

Lakshmi Nagarajan http://orcid.org/0000-0003-1608-6198

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