

REVIEW

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Acute symptomatic seizures in newborns: a narrative review

Carlotta Spagnoli^{1*}  and Francesco Pisani^{2,3}

Abstract

Acute symptomatic seizures are the main sign of neurological dysfunction in newborns. This is linked to the unique characteristics of the neonatal brain, making it hyperexcitable compared to older ages, and to the common occurrence of some forms of acquired brain injury, namely hypoxic-ischemic encephalopathy. In this narrative review we will provide an overview of neonatal seizures definition, their main underlying etiologies, diagnostic work-up and differential diagnoses, and will discuss about therapeutic options and prognostic outlook. The latest publications from the ILAE Task Force on Neonatal Seizures will be presented and discussed. Of note, they highlight the current lack of robust evidence in this field of clinical neurology. We will also report on specificities pertaining to low-and-middle income countries in terms of incidence, main etiologies and diagnosis. The possibilities offered by telemedicine and automated seizures detection will also be summarized in order to provide a framework for future directions in seizures diagnosis and management with a global perspective. Many challenges and opportunities for improving identification, monitoring and treatment of acute symptomatic seizures in newborns exist. All current caveats potentially represent different lines of research with the aim to provide better care and reach a deeper understanding of this important topic of neonatal neurology.

Keywords Acute symptomatic, Neonatal seizures, EEG, Newborn, Outcome, Diagnosis, Etiologies

Background

Seizures are the most common sign of neurological dysfunction in newborns. In a recent Italian paper, their incidence was found to correspond to 2.29/1000 live births, being higher in preterm (14.28/1000) than in full-term neonates (1.10/1000) [1]. Moreover, their incidence is inversely related to gestational age and birth weight [1, 2]. These figures are much higher, and more variable, in low/middle income countries (LMIC), where the incidence

is estimated to be as high as 36–90 per 1000 live births, although with an important bias deriving from clinically-based diagnosis [3].

The proneness of the immature brain to generate seizures is linked to a series of unique developmental features increasing its excitability compared to older ages and to the higher risk of newborns to sustain brain injury. The newborn brain is characterized by an imbalance of neuronal excitation over inhibition, deriving from age-dependent expression of excitatory glutamatergic receptors, ion channels, and transporters promoting excitation, while inhibition is relatively underdeveloped [4]. In human ontogenesis, excitatory synapses develop before inhibitory ones. Glutamatergic neurons are overabundant in the newborn brain, and their receptors' configuration allows relative hyperexcitability [5, 6]. In the neonatal brain GABAergic transmission has a depolarizing (excitatory) effect due to the expression of the

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Na–K-2Cl cotransporter 1 (NKCC1) [7–9], predating the expression of the mature potassium chloride cotransporter 2 (KCC2), responsible of the hyperpolarizing (inhibitory) effect shown at older ages under physiological conditions [9]. Additionally, in the first year of life synaptogenesis and dendritic spine density are at their peak [10, 11].

The second aspect is linked to hypoxia/ischemia being one of the most common forms of injury in the perinatal period, with developmentally regulated areas of major susceptibility and a unique ability of the immature brain to sustain and adapt to brain injury [4] (neuroplasticity).

Although this field is one of intense clinical and experimental research, many controversies and hurdles still exist in the recognition, monitoring and management of seizures in newborns.

In this narrative review, we wish to describe the definition, characteristics, diagnostic work-up, main differential diagnoses, management and outcome of acute symptomatic seizures in preterm and fullterm newborns, in light of the recent International League Against Epilepsy (ILAE) position papers, in order to provide and updated and practical framework for the clinician taking care of these fragile patients.

The search was made on PubMed by combining the following terms: “neonatal seizures”; “definition”; “classification”; “diagnosis”; “differential diagnosis”; “non-epileptic events”; “etiologies”; “therapy”; “treatment”; “outcome”. Only papers written in English and published in the last 20 years were included. This search was not intended to provide a systematic literature review, but rather to propose a general framework on the topic of acute symptomatic seizures occurring in neonates.

Definition

The ILAE Task Force on Neonatal Seizures proposed the latest definition of a neonatal seizure as “an electrographic event with a pattern characterized by sudden, repetitive, evolving stereotyped waveforms with a beginning and end. The duration is not defined but has to be sufficient to demonstrate evolution in frequency and morphology of the discharges and needs to be long enough to allow recognition of onset, evolution, and resolution of an abnormal discharge” [12].

Classification

Neonatal seizures were previously categorized as clinical-only, electroclinical, and electrographic-only [13]. However, clinical-only seizures are better categorized as non-epileptic events and therefore are no longer included in the classification. An electroclinical seizure features observable paroxysmal clinical phenomena time-locked with electroencephalographic (EEG) ictal discharges. Finally, electrographic-only seizures consist of the appearance of ictal EEG discharges without any overt clinical signs (also known as subclinical or clinically silent) [12]. In the latest classification, seizures are categorized according to their predominant clinical phenomenon into (Fig. 1): automatisms, clonic, epileptic spasms, myoclonic, tonic, autonomic (including paroxysmal cardiovascular, pupillary, gastrointestinal, sudomotor, vasomotor or thermoregulatory function abnormalities), behavioural arrest and sequential seizure. A sequential seizure is defined as “a sequence of signs, symptoms, and EEG changes at different times”, in which “no predominant feature can be determined, instead the seizure presents with a variety of clinical signs. Several features

ELECTROCLINICAL

Motor

Automatisms

Clonic

Epileptic spasms

Myoclonic

Tonic

Non-motor

Autonomic

Behavioural arrest

Sequential seizure

Unclassified

ELECTROGRAPHIC-ONLY

Fig. 1 Current ILAE classification of neonatal seizures

typically occur in a sequence, often with changing lateralization within or between seizures” [12].

Diagnosis

Diagnosis of neonatal seizures, per definition, requires an EEG recording, possibly with video and polygraphy [14] to detect ictal discharges and their clinical correlates with the highest sensitivity and specificity. For an optimal documentation of each subtle clinical phenomena, the use of additional cameras has been proposed [15]. As a matter of fact, in many neonatal units worldwide, conventional EEG (or the expertise to interpret it) might not be available 24h a day, 7 days a week, and thus amplitude integrated EEG (aEEG) has become the most readily available tool for immediate bed-side interpretation, being useful as a screening tool for seizure detection, for eligibility for therapeutic hypothermia in fullterm infants with hypoxic-ischemic encephalopathy (HIE) and to assist prognostication during the rewarming phase [16]. The correct interpretation of developmental EEG features and of ictal discharges requires specialized skills and some clinical scenarios, like EEG evaluation of a severely encephalopathic newborn with depressed background, might be particularly demanding. However, in selected cases, the holistic interpretation of EEG patterns and clinical semiology might allow identification of the most plausible etiology [17], helping to prioritize investigations and treatment choices. Infants born preterm or with severe encephalopathy more often have electrographic-only seizures, especially when they are on antiseizure, sedative, or paralytic drugs. Verifying any clinical suspicion with EEG before drug administration would be the best way to investigate these babies [18].

A different scenario is present in LMIC, where the availability of EEG or aEEG is limited, making seizures diagnosis even more challenging and also reducing the expertise to interpret EEG/aEEG data. As clinical diagnosis is not reliable because of the risk of both underdiagnosis and overdiagnosis [19], the following levels of certainty in formulating the diagnosis have been proposed:

1. **Level 1: Definite seizure** (seizures confirmed on EEG, with or without clinical manifestations).
2. **Level 2: Probable seizure** (clinically assessed focal clonic or focal tonic seizures or seizures confirmed on aEEG).
3. **Level 3: Possible seizure** (clinical events suggestive of epileptic seizures other than focal clonic or focal tonic seizures).
4. **Level 4: Not seizure** (reported clinical events that do not meet case definition).
5. **Level 5: Not seizure** (clinical events evaluated by EEG and diagnosed as not a seizure) [12].

Differential diagnosis

From an EEG point of view, the main differential diagnoses of neonatal seizures are with artefacts, which can be frequent in the busy and highly technological intensive care units, and require special care during both acquisition and interpretation [17, 20].

From a clinical point of view, paroxysmal clinical events in newborns can be due to brainstem release phenomena (i.e. generalized tonic events in preterm infants) or can correspond to a long list of paroxysmal movement disorders, which can represent “benign” self-limited (i.e. tremor, benign neonatal sleep myoclonus, startle reflex, hiccups), but also abnormal conditions (i.e. hyperekplexia, tongue fasciculations, neonatal dystonia) [21, 22], which might require dedicated diagnostic work-up and therapy, and are neither benign nor self-limited [23]. The first step to rule out an epileptic event is to perform a video-EEG, trying to capture several typical events. Paroxysmal non-epileptic events occurring in healthy newborns with normal neurological examination are expected to be self-limited and carry a favourable neurodevelopmental prognosis [24].

Etiologies

Seizures in the neonate can fall within two broad categories (Fig. 2): neonatal-onset epilepsies, which can be divided into genetic, metabolic, and of structural non-acquired origin (remote symptomatic or non-provoked seizures) [25, 26] and correspond to approximately 15% of all cases [27]; acute symptomatic seizures, which are provoked seizures, and occur as a consequence of an acute event causing cortical dysfunction (approximately 85% of all cases). Among the causes for this second type of event, which is the topic of this review, we can identify transient metabolic derangements and acute brain injury as the most significant categories. In the first group, electrolytes imbalance (calcium, sodium) and hypoglycemia always need to be ruled out, because they need specific therapies and usually do not respond to conventional antiseizure medications, which are usually not necessary provided that the primary derangement is efficaciously corrected. In this category, seizures secondary to hypoglycemia (especially if prolonged and severe) have a more complex pathophysiology, as occipital lobe injury can develop and result in a risk factor for long-term epilepsy [28]. Among acute brain injuries, the most frequent etiologies include HIE (especially in the fullterm or near-term newborn [29] and intracranial hemorrhage (in particular, intraventricular haemorrhage, especially affecting the very and extremely preterm newborn [30]). Additional causes include acute ischemic stroke, which is usually a type of injury affecting the fullterm or near-term infant, and acute central nervous system infection, which can

NEONATAL-ONSET EPILEPSIES*Genetic**Metabolic**Structural non-acquired***ACUTE SYMPTOMATIC SEIZURES***Transient metabolic derangements*

Hypocalcemia

Hyponatremia

Hypomagnesemia

Hypoglycemia

Acute brain injury

Hypoxic-ischemic encephalopathy

Intraventricular hemorrhage

Acute ischemic stroke

Acute central nervous system infections

Fig. 2 Main etiologies of seizures in newborns

occur at any gestational age and anytime during the neonatal period, and requires prompt diagnosis and initiation of specific therapies in order to prevent further complications [31].

Epidemiology differs in high-income countries (HIC) as opposed to LMIC. While HIE is the main cause in both areas, even if the incidence is higher in LMIC, infections are the second most common cause in LMIC, whereas intracranial hemorrhage and perinatal stroke are less frequently diagnosed, possibly because of reduced access to neuroimaging. Finally, nowadays acute metabolic abnormalities are more common in LMIC because their incidence in HIC significantly decreased in the latest decades thanks to the improvements in newborns' clinical care [3].

Diagnostic work-up

Neonates with confirmed seizures should be thoroughly investigated, as it is not uncommon for individual patients to have more than one predisposing factor/underlying etiology [3, 31].

History taking should focus on birth, and maternal, fetal and family factors. Relevant history related to birth includes complications during, prior or immediately after delivery, such as cord prolapse/thrombosis, placental abruption, uterine rupture, non-reassuring fetal heart rate, meconium aspiration, low Apgar scores, placental abnormalities, planned home birth, operative vaginal delivery, or abnormal fetal presentation. Relevant maternal medical history can include, for example: previous miscarriages, gestational diabetes or pre-eclampsia, infections, prenatal exposure to/withdrawal of prescription or illicit drugs, presence of inherited thrombophilias or bleeding disorders. Family history can include early sibling's death or cases of epilepsy or other neurologic disorders [32, 33].

The timing of seizure onset can suggest specific etiologies: seizures occurring within 12–24 h after birth suggest hypoxic-ischemic encephalopathy, while seizures starting afterwards may indicate infection, hemorrhage, stroke [22] or a genetic cause.

Physical examination can be helpful in checking head size, presence of micro/macrosomia, dysmorphisms, and somatic abnormalities [32], with the aim to identify clues for the underlying condition. General appearance, vital signs, level of alertness, and fontanelle characteristics might suggest bacterial meningitis, septic shock or acute intracranial hemorrhage [34]. Auscultation over the fontanelle can also disclose artero-venous malformations [33]. Skin examination can disclose findings suggestive of a congenital infection, and enables evaluation of perfusion. Acute metabolic acidosis, poor feeding, lethargy, and respiratory distress after a symptom-free period are typical presentations of inborn errors of metabolism [33, 35]. A thorough neurological examination can suggest signs of central or peripheral nervous system involvement, signs of encephalopathy, presence of focal neurological signs.

In addition, placental pathology can be used to detect signs of infection or perinatal insults [31].

Initial laboratory tests should include a complete blood count, glycemia, electrolytes [36] (to rule out: hypoglycemia, hyponatremia, hypomagnesemia, hypocalcemia), urine culture and toxicology, TORCH (toxoplasmosis, rubella cytomegalovirus, herpes simplex, and HIV) screening, metabolic screening, and ophthalmologic evaluation. CSF analysis, blood culture, C reactive protein are basically requested to rule out sepsis/meningitis/encephalitis [32].

Cranial ultrasound scan is a readily available, valuable bed-side diagnostic tool, especially for intracranial hemorrhages and their complications (i.e. post-hemorrhagic

hydrocephalus), but also useful in case of arterial stroke, malformations or infections. It should be considered as a routine investigation in acute symptomatic seizures, and it should be performed as soon as possible [36].

However, if available, all newborns with seizures should have brain magnetic resonance imaging (MRI) as soon as they are stable enough [18]. Brain MRI with diffusion is the gold standard, enabling identification of the main causes of seizures in newborns, such as hypoxic-ischaemic injury, arterial and venous stroke, meningitis/encephalitis, and malformations [36].

If the newborn has difficulty controlling seizures or exhibits additional symptoms and signs, inborn errors of metabolism and genetic neonatal-onset epilepsies should be considered, and further investigations should be tailored based on clinical suspicion/presentation. A blood gas analysis, ammonia, pyruvate, lactic acid, aminoacids and urine organic acids, very long chain fatty acids, biotinidase, pipercolic acid, CSF lactate, amino acids and pyridoxal-phosphate might all be considered on a case-by-case basis [32]. Genetic testing might include microarray, next generation sequencing with targeted panels or whole exome sequencing (WES) and whole genome sequencing (WGS) (Fig. 3) [37]. However, in HIC, due to the growing availability of NGS technologies, and their progressively reducing turnaround times and costs,

directly performing WES/WGS is becoming more and more common, due to their positive cost-effectiveness profile. In fact, the clinical impact of reaching the exact diagnosis in NICUs is high, resulting in a management change in more than 50% of tested patients [38–40]. The usefulness of rapid NGS sequencing also include the opportunity to clarify confounding phenotypes in light of dual diagnoses and “solve “atypical phenotypes [41]. Directly accessing WES or WGS can allow bypassing neurometabolic testing and invasive procedures (i.e. lumbar puncture) in the early phases of the diagnostic work-up. The potential applications of NGS in newborns are also being evaluated in the field of newborn screening (NBS) programs. Although DNA sequencing cannot substitute for current conventional screening due to insufficient sensitivity and specificity, it can be beneficial during follow-up, by resolving inconclusive NBS results, distinguishing the correct disorder in cases of ambiguous NBS results, and by decreasing the numbers of follow-up samples required reducing follow-up of false positive results and by identifying disease diagnosis [42].

Neuromonitoring

In the field of acute symptomatic seizures, the optimal timing and strategies to monitor high-risk newborns have been detailed for preterm infants and for full-term

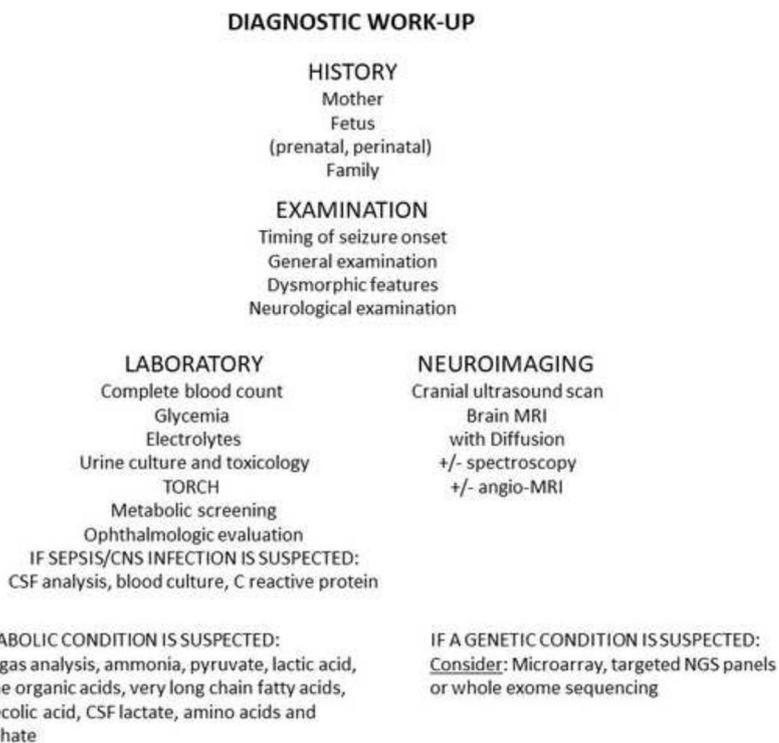


Fig. 3 Diagnostic work-up for seizures in newborns

and near-term newborns with HIE [43–45]. Whenever possible, we recommend a multimodal approach [46] integrating aEEG, conventional EEG, ultrasound brain scanning, brain MRI and evoked potentials, and (ideally) near-infrared spectroscopy (NIRS) [16]. A more tailored approach is advisable for neonatal-onset epilepsies [25].

Multichannel continuous EEG

Reliable diagnosis of seizures in newborns can only be achieved with continuous EEG monitoring of at-risk neonates [47]. Furthermore, screening of at-risk newborns allows optimal management, as prompt treatment initiation can result in better response to antiseizure medications compared to performing a confirmatory EEG after clinically suspected seizures [48].

High-risk neonates should be monitored for 24 h, even though the correct monitoring duration may vary according to clinical setting and previous EEG data. Once seizures are recorded, it should continue for at least 24 h after their resolution [49], in order to confirm that they truly abated with antiseizure medications [50, 51].

Amplitude-integrated EEG (aEEG)

The aEEG is a useful, non-invasive, bedside monitoring tool used to evaluate brain function (i.e. before hypothermia), background activity, and sleep-wake cycling [52] (which are all prognostic predictors) [53]. Its use in seizure diagnosis has some limitations [52]. When a one-or-two-channel aEEG is used without synchronous raw EEG trace reading, sensitivity is slow (27–56%) [54]. The sensitivity and specificity of raw aEEG for the detection of neonatal seizures have been reported to range from 68% to 84% and 71% to 84%, respectively, and it is worth noting that these values strongly depend on the user's level of experience [55]. With advanced training, up to 60–90% of newborns with seizures can be identified, although not all individual seizures might be detected, especially if the seizures are very focal, brief or distant from the scalp area covered by the electrodes [56]. Inter-observer agreement is lower than with conventional EEG, but combining a two-channel aEEG with raw EEG can enhance diagnostic accuracy [57]. In a prospective quality improvement cohort study, aEEG and conventional EEG were concurrently recorded, and the neonatal intensive care unit (NICU) staff interpreting aEEG had the option to contact an on-call neurologist for real-time conventional EEG interpretation [47]. This resulted in a 27% increase in correct seizure identification and avoidance of over-diagnosis in 33.3% of cases [58].

In low-resource settings, telemedicine may provide remote specialized assistance [3], as exemplified by the Protecting Brains and Saving Futures project in Brazil, where over 20 hospitals were involved in EEG or aEEG

monitoring, with the on-site team being assisted by a remote specialized team, who supplied educational activities, consultation, and monitoring. Encrypted EEG data were sent to a secure cloud-based server, and access to the monitoring system, management of backup and security services were all available through authentication. However, legal and regulatory issues, but also feasibility (in terms of cost-effectiveness) would need further evaluation before such an approach can be implemented in LMIC [59]. Additionally, this is a way to initially provide and subsequently build the necessary expertise for monitoring, but equipments need to be on site, and the relative resources to be allocated.

Automated neonatal seizure detection

Along with telemedicine, other ways to solve the issues related to the lack of around the clock availability of neonatal EEG expertise in NICU's, are represented by automated detection systems and artificial intelligence [60].

Automated detection systems can assist in background grading and/or seizures recognition, either with video, EEG or other biological signals' analysis. The topic has been recently reviewed [61]. Among EEG-based systems, different approaches can be identified: heuristic algorithms (based on an empirical definition of rules, thresholds, and parameters, and on the search for variations in signal trends [62–64]), data-driven algorithms (based on machine learning techniques, in which features, rules and thresholds are learnt during data acquisition in the training phase) [65–67], deep-learning algorithms (which extract information from data and learn abstract representations features [68–70]), electrocardiogram (ECG)-based systems (assessing changes in inter-beat time intervals, or heart rate variability – HRV) [71–75], and video-based systems [76–83], which are not intended to substitute interpretation of EEG signal but might be integrated into multiparametric detection systems.

So far a single multicentre, randomized, controlled trial has been published on the subject. It compared conventional EEG plus the Algorithm for Neonatal Seizure Recognition (ANSeR) versus conventional EEG monitoring alone. ANSeR was linked to the EEG monitor, and displayed a seizure probability trend in real time. While the algorithm did not improve identification of individual newborns with seizures, it improved recognition of seizure hours (i.e. the total duration of seizures was better clarified). The authors thus hypothesized better advantages in less experienced centres [67]. Some of these algorithms are commercially available [82–85]. Artificial intelligence is being increasingly proposed as an instrument to overcome the complexity of interpreting EEG for neonatal seizures diagnosis. In a recent study, EEG is converted to sound, so that the perceptual characteristics

of seizures can be heard and interpreted by medical personnel with little or no expertise in neonatal neurophysiology, with an accuracy similar to that of trained neurophysiologists and higher than that of artificial intelligence alone [86].

Therapy

A part from correcting acute electrolytic and metabolic derangements, clinical practice on the treatment of neonatal seizures with antiseizure medications may differ according to subspecialty (i.e. neonatologists versus pediatric or neonatal neurologists), and according to seizure etiology, reflecting the lack of robust evidence from the literature and the persistence of knowledge gaps, especially for the management of preterm infants. A multicentre Italian survey among pediatric neurologists working in third level NICUs documented that the most commonly suggested sequence of antiseizure medications in case of acute symptomatic seizures was: phenobarbital (79%), phenytoin (58%), midazolam (42%), and levetiracetam (42%), while for neonatal seizures due to a genetic or structural epilepsy, the concordance among pediatric neurologists was lower [87].

This can be partially explained by the many controversies surrounding phenobarbital, which is only effective in approximately half of the cases [88], causes electroclinical uncoupling and can have relevant adverse effects, such as hypotension, sedation and respiratory suppression [89] which might be particularly relevant in critically-ill newborns [90]. Finally, experimental data suggest a negative effect on neuronal apoptosis [91] and synaptic maturation [92].

These considerations have led to increasing off-label prescription, especially of levetiracetam [93], thanks to its good safety profile [94], although efficacy seems to be lower than that of phenobarbital [90]. In particular, in one study recruiting 38 newborns, receiving levetiracetam as first-line, 19 newborns had one dose of phenobarbital and 3 received two phenobarbital doses due to lack of seizure control on levetiracetam. At the end of the first week, however, 30 neonates were seizure free on levetiracetam and 27 were still seizure free at four weeks [95]. A multicenter, randomized, blinded, controlled trial randomly assigning newborns to phenobarbital or levetiracetam as first-line treatment documented 80% seizure freedom for 24 h on phenobarbital versus 28% on levetiracetam, with a 7.5% improvement in efficacy with levetiracetam dose escalation to 60 mg/kg [89]. Subsequently, other groups documented more encouraging results [96]. A systematic review and meta-analysis of studies evaluating levetiracetam as the first-line treatment of neonatal seizures in preterm and full-term infants analyzed 14 studies assessing

1188 newborns. Pooled efficacy with levetiracetam from observational studies was 45%, while meta-analysis of randomized controlled trials comparing it with phenobarbital showed equal effectiveness, but lower risk of short-term adverse events with levetiracetam [97]. As acute symptomatic seizures tend to spontaneously abate with time, it is noteworthy to also investigate response rate as add-on. One recent retrospective study evaluated efficacy of levetiracetam administered as a 2nd-to-4th-line to near term newborns not responding to first-line phenobarbital. Efficacy was defined as >80% seizure reduction. This was obtained in 17% of newborns on levetiracetam, versus 23% after midazolam and 92% after lidocaine [98], arguing in favour of further, prospective research involving homogeneous populations in terms of gestational ages and etiologies, and with definite protocols for seizures monitoring.

Recently, the ILAE Task Force on Neonatal Seizures published evidence-based and consensus-based recommendations for treatment, which can be summarized as follows. Phenobarbital should be the first-line treatment, irrespective of seizures etiology, unless a channelopathy is suspected, in which case sodium channel blockers such as phenytoin and carbamazepine should be administered. If neonates do not respond to the first-line drug, phenytoin, levetiracetam, midazolam, or lidocaine may be used as a second-line [88, 89, 99]. Levetiracetam was recommended (based on expert opinion) in newborns with cardiac diseases, due to potential for cardiotoxic effects of alternative second-line drugs (i.e. phenytoin, lidocaine) [100]. Based on expert opinion, pyridoxine might be trialed if clinical features of vitamin B6-dependent epilepsy are present and when seizures do not respond to second-line medications. These recommendations highlight the current lack of robust evidence on the therapeutic management of seizures in newborns, especially beyond first-line management (Fig. 4).

According to a recent Cochrane review, if seizures cease after the first loading dose of phenobarbital, maintenance therapy compared to no maintenance may have little or no effect on mortality before discharge, mortality or neurodevelopmental disability by 18–24 months and epilepsy post-discharge [101]. In neonates with HIE, treatment of both clinical and electrographic-only seizures compared to clinical seizures alone may have little or no effect on seizure burden during hospitalisation, mortality before discharge and epilepsy post-discharge [101]. However, caution should be expressed, as the level of evidence is low and some literature data indeed seem to support the notion that electrographic-only seizures can be just as detrimental as electroclinical seizures [102].

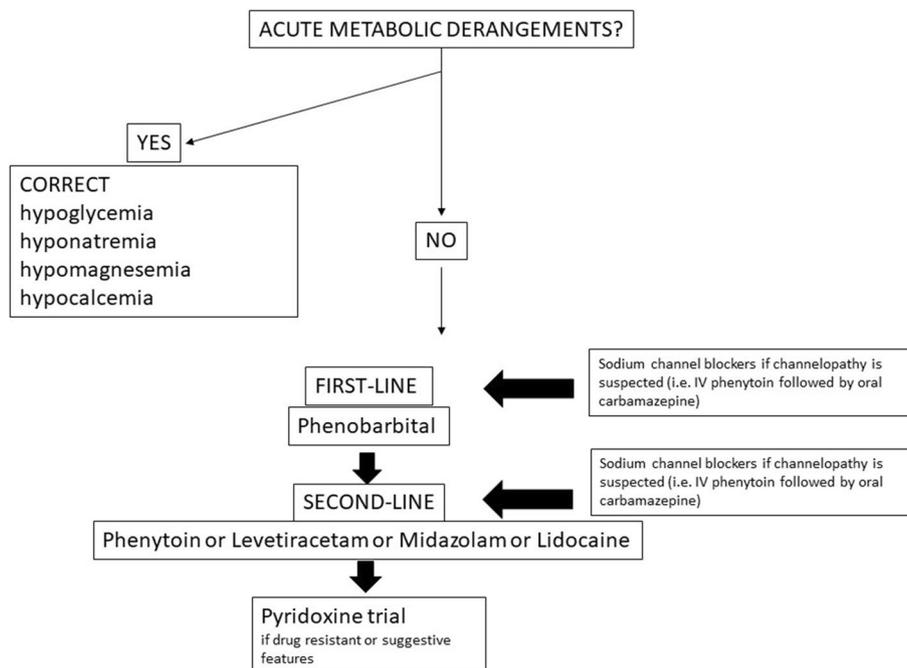


Fig. 4 Flow-chart for seizures treatment (modified from Gotman J, et al [84])

Additionally, prolonged or recurrent seizures might worsen brain injury beyond that of the underlying etiology [103, 104], a notion that is sustained by both experimental and clinical data [103–107]. A recent study documented a significant negative correlation between seizure burden and developmental scores, and this association was stronger for HIE and stroke [108]. Prompt recognition of seizures can result in higher drug response [88, 89]. As an example, neonates treated within 1 h of seizure onset had lower seizure burden and fewer seizures in the following 24 h, suggesting that the impact of antiseizure medications on seizure burden is time-critical [66]. However, the optimal timepoint for treatment initiation is yet to be defined [90]. A cumulative electrographic seizure burden of more than 30 s/h was proposed as an entry criterion in therapeutic trials [109].

Factors associated with lack of response to antiseizure medications have been seldom investigated. They include higher seizure frequency, particularly status epilepticus [110], electrographic-only seizures, and abnormal EEG background [111], higher mean seizure score and higher degrees of brain MRI injury (white matter, cortex, and watershed regions) [112].

Outcome

Acute symptomatic seizures in newborns are frequently followed by the occurrence of various unfavorable outcomes, including death, cerebral palsy, epilepsy,

intellectual disability, vision and hearing impairment, and microcephaly [103, 112–115].

Mortality is higher in preterm (32–35%) than in full-term newborns (5.4–15%) [103, 116–118]. In a systematic review on papers investigating the outcome of preterm infants with seizures published in the 2000’s, we found a 11.3–38.9% occurrence of epilepsy, a 12–84.6% of cerebral palsy, and a 20–42.7% of intellectual disability or developmental delay. When a comparison group without seizures was present, outcome was worse in infants with seizures [119].

Outcome clearly changes according to birth weight and gestational age. Mortality of preterm infants with seizures increases in patients with a birth weight < 1000 g and a gestational age < 28 weeks [120]. Among preterm infants with seizures evaluated at the mean age of 6.2 ± 2.0, years, 44.4% of the very low birth weight (VLBW) group and 71.4% of the low birth weight (LBW) group showed intellectual impairment, while cerebral palsy was present in 22% of VLBW and 42.9% of LBW infants. Postneonatal epilepsy was present in 11.1% of VLBW infants and 28.5% of LBW infants [121].

Data on full-term newborns report 17% of cerebral palsy [122], 35% of intellectual disability [123], and 10–15% of epilepsy [124] in NICU-based series, which collect information on the most severely affected newborns.

Epilepsy most often starts early, occurring within the first year of life in 68.5% of cases [125], except in case of perinatal arterial ischemic stroke, where the age at the first post-neonatal seizure ranges from 1 to 10 years, but the latent period can be as long as 15 years [126]. The rate of epilepsy following perinatal stroke is around 16%, and infarct location (right middle cerebral artery; multiple involved territories) is a negative independent predictor [127].

In full-term and near-term infants with moderate-to-severe HIE, the use of therapeutic hypothermia has significantly changed the outcome of these newborns. In fact it is associated with an increase in survival with normal neurological exam, and it significantly lowers the risk of cerebral palsy, moderate/severe disability and epilepsy [128]. However, still almost half either die or suffer from severe neurodevelopmental disabilities, while 40% have a normal neurodevelopmental outcome [129]. Neurologic sequelae can range from mild to disabling. Cerebral palsy develops in 13% of cases [130], while an IQ score below 70 is found in 96% of children with cerebral palsy and in 9% without [131]. The percentage of infants with abnormal outcome is higher in those presenting with neonatal seizures: 62% versus 39% [105].

The current prognostic outlook of seizures in LMIC has different characteristics and specific challenges compared to high income countries. These include (among others) mortality rates, compliance to scheduled pregnancy evaluations, epidemiology regarding etiologies, availability of EEG and frequent clinical definition of seizures. Mortality rate differs according to studied populations and geographical areas. Mortality in the neonatal period is reported to vary [132–136] between 7.8% [2] and 32.51% [137]. The occurrence of additional deaths after the neonatal period was reported to correspond to 3.94% in [137] and to 9.1% in [133]. Interestingly, a study from a rural area in Kenya found no differences based on the occurrence of seizures, but a different profile risk based on birth weight, with a detrimental role of seizures in newborns over 2500 g [133], possibly outlining the predominance of other (stronger) determinants of unfavourable outcome in the low birth weight group, pointing out to a need for addressing different management objectives in these babies. At discharge, 10–13% of the surviving neonates have an abnormal neurological exam [132, 133], and 8.4% severe neurologic deficits [135]. In a study performed in India, 26.1% of survivors had abnormal neurological examination at discharge, either in the form of abnormal tone (20.3%), reflexes (14.4%) or consciousness (7.2%) [134].

Identifying the main factors determining outcome is crucial for the correct management of newborns and correct counseling to the families. Among the most

important prognostic factors we can include: antenatal—including placental—factors (i.e. chorioamnionitis) and multiple perinatal factors, such as gestational age, Apgar scores, prolonged resuscitation, birth weight, etiology (HIE and intraventricular hemorrhage [IVH] carrying the worst prognosis), severity and patterns of brain injury, neurological examination, presence of a congenital heart disease [138] and abnormal background EEG [139–142].

However, among these, the most important roles are played by etiology, and location and severity of brain injury. In hypoxic-ischemic encephalopathy, brain MRI patterns of injury predict the severity and type of neurodevelopmental sequelae [143–145]: basal ganglia–thalamic and brainstem injury are often associated with the severest impairments (cerebral palsy, cognitive impairments and epilepsy), whereas watershed type of injury mostly affects cognitive development [143–147].

However, seizure-related factors are also critical. Longer seizure duration, higher seizure burden [143] and especially the occurrence of status epilepticus are important determinants [105, 140, 142, 148]. In detail, spreading of the ictal discharges to the contralateral hemisphere, status epilepticus [118, 141], a family history of epilepsy, abnormal neurological examination at discharge [149], poor response to anticonvulsants [124], and the use of at least two antiseizure medications represent risk factors for later epilepsy [149]. The latter variable also relates to severe neurodevelopmental delay in fullterm infants [150] and to the risk of death and poor outcome in hypoxic-ischemic encephalopathy [151, 152]. Additionally, in infants with hypoxic-ischemic encephalopathy, although the presence of seizures per se was not associated with abnormal outcome, a total seizure burden exceeding 40 min and a maximum hourly seizure burden of more than 13 min were associated with unfavourable outcome, independently of electrographic grade of HIE or therapeutic hypothermia. In any case, it would be useful to collect further data on outcome determinants in newborns with specific etiologies and possibly controlled for degree of brain injury, and to study populations of newborns outside the better known subgroup of newborns with hypoxic-ischemic encephalopathy.

Conclusions

Seizures in newborns are a frequent phenomenon, and need to be: correctly interpreted, documented and monitored; promptly and efficaciously treated; thoroughly investigated. Each of these steps is time-consuming, and requires specialized skills and dedicated resources (in terms of personnel and devices). Thus, delivering the best possible care to high-risk and critically ill newborns is challenging. However, this is critical to improve survival and long-term outcome. These

challenges can be dealt with at different levels: from promoting education and building specialized expertise, to developing telemedicine programs; from organizing clinical trials in order to collect robust evidence, to supporting preclinical research on many controversial topics. In the mean time, the international effort to uniform glossaries, taxonomy and monitoring and to provide state-of-the-art guidance for treatment is an important way to disseminate better standards of care.

Abbreviations

aEEG	Amplitude-integrated EEG
ANSeR	Algorithm for Neonatal Seizure Recognition
CSF	Cerebrospinal fluid
ECG	Electrocardiogram
EEG	Electroencephalogram
HRV	Heart Rate Variability
ILAE	International League Against Epilepsy
IVH	Intraventricular hemorrhage
LMIC	Low/middle income countries
KCC2	Potassium Chloride Cotransporter 2
NKCC1	Na–K–2Cl cotransporter 1
HIC	High-income countries
HIE	Hypoxic-ischemic encephalopathy
MRI	Magnetic resonance imaging
NICU	Neonatal intensive care unit
NIRS	Near-infrared spectroscopy

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Authors' contributions

C.S. and F.P. conceived the study design and collected the relevant literature. C.S. wrote the first draft of the manuscript. F.P. critically reviewed the paper for intellectual content. C.S. and F.P. approved the paper in its final form.

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