



## Review

## Seizures in the neonate: A review of etiologies and outcomes

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## ABSTRACT

Neonatal seizures occur in their majority in close temporal relation to an acute brain injury or systemic insult, and are accordingly defined as acute symptomatic or provoked seizures. However less frequently, unprovoked seizures may also present in the neonatal period as secondary to structural brain abnormalities, thus corresponding to structural epilepsies, or to genetic conditions, thus corresponding to genetic epilepsies. Unprovoked neonatal seizures should be thus considered as the clinical manifestation of early onset structural or genetic epilepsies that often have the characteristics of early onset epileptic encephalopathies. In this review, we address the conundrum of neonatal seizures including acute symptomatic, remote symptomatic, provoked, and unprovoked seizures, evolving to post-neonatal epilepsies, and neonatal onset epilepsies. The different clinical scenarios involving neonatal seizures, each with their distinct post-neonatal evolution are presented. The structural and functional impact of neonatal seizures on brain development and the concept of secondary epileptogenesis, with or without a following latent period after the acute seizures, are addressed. Finally, we underline the need for an early differential diagnosis between an acute symptomatic seizure and an unprovoked seizure, since it is associated with fundamental differences in clinical evolution. These are crucial aspects for neonatal management, counselling and prognostication. In view of the above aspects, we provide an outlook on future strategies and potential lines of research in this field.

## 1. Introduction

Seizures are the most frequent neurological sign observed in the neonatal intensive care unit and occur in their majority in close temporal relation to an acute brain injury or systemic insult, with or without identifiable structural abnormalities [1]. These events are defined as acute symptomatic or provoked seizures. Although these two terms are often used interchangeably, acute symptomatic seizures are in fact defined as resulting from an acute brain injury, such as stroke, trauma or brain infection, whereas provoked seizures are defined as resulting from transient and reversible brain alterations of metabolic or toxic origin [2].

Though less frequently, unprovoked seizures may also present in the

neonatal period [3]. These are defined as seizures occurring in the absence of a potentially causative clinical condition or beyond the interval estimated for the occurrence of acute symptomatic seizures [4]. Unprovoked seizures can be secondary to structural brain abnormalities, such as malformations of cortical development and prenatal ischemic lesions [5,6], thus corresponding to structural epilepsies, or to genetic conditions, such as ion channel and vitamin-dependent disorders, thus corresponding to genetic epilepsies [7]. Of note, the latest, multi-parametric and non-mutually exclusive etiologic classification of the epilepsies by the ILAE [7], has included the increasingly appreciated genetically-determined structural epilepsies, at the interface of genetics and focal, surgically remediable epilepsy [8].

**Abbreviations:** ILAE, International League Against Epilepsy; aEEG, amplitude-integrated EEG; CDG, congenital disorders of glycosylation; HIE, hypoxic-ischemic encephalopathy; HSV, herpes simplex virus; JAK/STAT, Janus kinase/signal transducer and activator of transcription; mTORC, mammalian target of rapamycin; trkB, tyrosine receptor kinase B; PLCc1, phospholipase Cc1; TLR4, Toll-like receptor 4; HFO, high-frequency oscillations.

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## 2. Overall incidence of neonatal seizures

Irrespective of their classification as acute symptomatic events or as manifestations of a neonatal-onset epilepsy, neonatal seizures occur with an estimated incidence of 1/1000 to 5/1000 live births in population-based studies [9–14] but a 8.6/1000 rate in a NICU-based study [15], with considerably higher rates for preterms. In addition, the incidence of neonatal seizures is hard to define, since the majority of epidemiological studies derive from clinical observation alone [9,10,16] that is known to be often unreliable [17]. Recently, in an epidemiological study considering only EEG-confirmed neonatal seizures [18], a 5.0/1000 incidence was reported for neonates of 31–36 weeks of gestation, 54.9/1.000 for those of 28–30 weeks of gestation, and 85.6/1000 for neonates of <28 weeks of gestation. Furthermore, the risk of neonatal seizures is increasing with decreasing birth weight [19]. It should be noted that the discrepancy in the incidence rates of neonatal seizures between different studies is due not only to disparities in the gestational age and birth weight of affected neonates, but also to disparities in the applied diagnostic criteria.

## 3. Limits in diagnosing neonatal seizures

Many studies, particularly in the past decades, lack the verification of video-EEG recordings for the diagnosis of neonatal seizures [20,21]. However, EEG-confirmation is absolutely mandatory to avoid misdiagnosis, particularly in preterm infants with their wide spectrum of uncoordinated movements especially in sick term neonates, considering the frequently subtle seizure semiology [22–24]. The high rate of uncoupling, with an abundance of electrographic only seizures in affected neonates, adds to this challenge [25–27]. The majority of neonatal seizures are subclinical and thus only identified by their EEG signatures [3].

Continuous EEG monitoring is clearly the only means to reliably detect neonatal seizures, promptly initiate their treatment, and monitor treatment success [28]. EEG traces with clear and sustained discharges of >10 s duration indicate electrical or electro-clinical seizures [29] and ictal EEG patterns are often focal in origin, while not necessarily corresponding to an underlying focal pathology [30]. An integrative approach to neuromonitoring in high-risk neonates with simultaneous video-EEG recording and, ideally, a multicamera setup instead of the standard single-camera, can significantly increase diagnostic accuracy [31]. However, continuous EEG monitoring is expensive, time-consuming, and moderately invasive, while its real-time interpretation is prohibitive, since it would require particularly skilled medical personnel to be available around-the-clock in neonatal intensive care units [32].

In light of these limitations, amplitude-integrated EEG (aEEG) has gained ground in the last decade, as it is readily available, less invasive, easy to set-up, and enables prolonged recordings. aEEG is very effective in the detection of prolonged seizures and status epilepticus [33], but may miss brief and focal seizures as well as those associated with low-amplitude ictal EEG patterns that constitute a significant proportion of neonatal seizures, particularly in preterms [34–36]. In addition, recently developed seizure detection algorithms deriving from EEG and EKG data [37], from EEG data alone [38–40], or from movement analysis [29,41–43], have the potential to overcome the hurdles of continuous EEG monitoring interpretation, and facilitate as well as expedite the diagnosis of neonatal seizures by providing a real-time decision support. Overall, automated seizure detection is promising, but still requires validation for use in everyday clinical practice.

## 4. Acute symptomatic seizures

Acute events leading to brain injury, such as hypoxic-ischemic encephalopathy (HIE), cerebral infarction, and haemorrhage, are responsible for the vast majority of acute symptomatic seizures in neonates,

accounting for approximately 75 % of cases in term neonates [44–46]. Intraventricular haemorrhage represents the most frequent aetiology in preterms, ranging from 16 % to 45 % of cases. Acute, transient brain dysfunction is the underlying cause of seizures in neonates with drug-related side-effects, acute withdrawal from toxic drugs or transient metabolic disorders, though these cases have drastically decreased in the last decades due to improvements in neonatal care [47].

In 84 % of term neonates, acute symptomatic seizures occur within the first three days of life [44]. The *condicio sine qua non* in these clinical scenarios is the presence of an identifiable aetiology which is temporally related to the seizure onset. In fact, the distinction between acute and remote seizures is based on the time of seizure onset with respect to the causal event: while acute seizures have an onset up to one week after a known event, remote seizures occur later on [4]. However, this temporal distinction between acute and remote seizures in neonates is particularly challenging, as structural or metabolic neonatal epilepsies can also present with a seizure onset in the first week of life. It should be noted that, although neonates with acute brain injury have an increased risk of developing post-neonatal epilepsy due to secondary epileptogenesis [48, 49], by definition acute symptomatic seizures are unlikely to recur, unless the underlying acute causal condition recurs [50].

## 5. Neonatal epilepsy vs. remote symptomatic seizures

While the majority of neonatal seizures is related to acute brain injury, about 15 % of neonates feature neonatal epilepsy syndromes, due to either congenital brain malformations in 41 %, or to genetic aetiologies in 42 % of this subgroup, with a 9% overlap between structural and genetic aetiologies [51]. In this light, unprovoked neonatal seizures should be considered as the clinical manifestation of early onset epilepsy, of structural or genetic origin that have the characteristics of epileptic encephalopathies. High-resolution neuroimaging in the first weeks of life [52], together with a thorough biochemical screening [53] and genetic workup [54] are essential for the identification of the underlying aetiology, the initiation of the optimal treatment, and for counselling and prognostication in neonatal epilepsies [3].

The two epilepsy syndromes with neonatal onset recognized by the ILAE [7], early infantile epileptic encephalopathy with burst-suppression (Ohtahara syndrome) and early myoclonic encephalopathy, are of structural or genetic/metabolic origin, with Ohtahara syndrome most usually attributable to structural and early myoclonic encephalopathy to genetic/metabolic causes. These neonatal epilepsy syndromes present with distinct EEG patterns and seizure types, they are highly refractory, and carry an adverse prognosis [55–58]. Early-onset electroclinical syndromes of genetic origin are overall relatively rare, accounting for up to 6% of neonatal seizures [51], but they are invariably associated with a high seizure burden, poor response to treatment, mortality, and significant morbidity with severe neurodevelopmental outcomes. Only the so-called benign, self-limiting familial neonatal epilepsy [59–62], associated with pathogenic variants in two potassium channel subunit genes, is expected to resolve within the first year of life. Most patients with benign familial neonatal epilepsy develop normally, although some affected individuals develop intellectual disability that becomes noticeable in early childhood [63].

Inborn errors of metabolism, such as antequitin- and PNPO-deficiency, congenital hypophosphatasia, molybdenum cofactor deficiency, isolated sulfite oxidase deficiency, neonatal non-ketotic hyperglycinemia, organoacidurias, congenital disorders of glycosylation (CDG), Zellweger syndrome, and adenylosuccinate lyase deficiency [3] present with seizures in early life that should be appreciated in the context of early-onset genetic epilepsies with a neurometabolic origin. Early diagnosis according to a standardised diagnostic algorithm is crucial, since it enables specific treatment in some of these metabolic early onset neonatal epilepsies [3,64], otherwise seizures are commonly drug-resistant and outcome is often adverse [65–67].

Structural epilepsies on the ground of neuronal migration disorders,

such as tuberous sclerosis, focal cortical dysplasia, hemimegalencephaly, lissencephaly, subcortical band heterotopia, periventricular nodular heterotopia, schizencephaly and polymicrogyria, have been increasingly recognised as neonatal seizure substrates due to advanced neuroimaging [68] and account for 5–9 % in contemporary cohorts [44,51]. These patients feature catastrophic drug-resistant epilepsies with high morbidity and mortality rates and should be identified at an early stage based on seizure semiology, EEG findings and high-resolution neuroimaging, since they may be excellent candidates for epilepsy surgery [6,69–71]. Early presurgical evaluation and surgical intervention for structural epilepsies in this age group is crucial [54], since, beyond seizure freedom in the majority of children, treatment success translates in optimal cognitive development [72].

It should be noted that one third of neonates with brain malformations as their primary seizure aetiology may also feature acute brain insults, such as HIE or cerebral infection, that in turn predispose to acute symptomatic seizures [51]. This observation underlines the need for comprehensive diagnostics in neonates with seizures, in order to differentiate neonatal onset epilepsies from acute and, later, remote symptomatic seizures. Neuroimaging, together with pre- and perinatal history, electroclinical features and neurological examination, can play an important role in the differential diagnosis [73,74], as it can highlight the pattern and extent of brain injury, characterize it as either pre-, peri- or postnatal, suggest its nature as acquired, congenital (i.e. cortical malformations), or genetic.

## 6. Clinical scenarios in the neonatal period

Neonatal seizures are a frequent clinical manifestation in the neonatal period and they can present within the framework of four clinical scenarios, each with a distinct post-neonatal evolution (Fig. 1). In scenarios A, C, and D, neonatal seizures correspond to acute symptomatic seizures that may be self-limiting (A), initially stop but eventually evolve after a latent period in post-neonatal epilepsy (C), or never stop, but directly evolve to post-neonatal epilepsy (D), whereas in scenario B, neonatal seizures correspond to the first manifestation of early-onset structural or genetic epilepsy.

It should be noted that, although these four scenarios for neonatal seizure presentation are conceptually useful, in practice the categorization of patients into the scenarios A, B, C or D may not be possible until well into the post-neonatal period. In addition, the same aetiology (e.g. HIE), can result in different clinical expressions depending on the injury severity, other co-morbidities, or underlying genetic factors.

**A. Acute symptomatic seizures clearly related to an acute brain insult and thus self-limiting.** In particular, neonatal seizures occurring up to 72 h

after birth are predominantly acute symptomatic, and may be associated with stroke, bacterial meningitis, intrauterine infection, intraventricular haemorrhage in preterm neonates, drug withdrawal, and metabolic perturbances [75]. These neonatal seizures usually stop a few days after their onset, i.e. a few days after the acute brain insult, regardless of the therapeutic intervention. Early identification of the precipitating insult (s) is mandatory and the required treatment should be started promptly. These neonates do not have an enduring predisposition to recurrent seizures, therefore prolonged treatment, after the acute stage, is not required [76].

**B. Unprovoked seizures/remote symptomatic seizures, secondary to structural brain abnormalities or to a genetic condition.** These neonatal seizures correspond to structural or genetic epilepsies with onset in the first days of life. They usually respond poorly to antiseizure-drugs that cannot be withdrawn at discharge in most cases. These epilepsies are defined by the ILAE as occurring in the absence of a potentially responsible acute clinical condition or beyond the interval estimated for the occurrence of acute symptomatic seizures [7]. In fact, epilepsy is defined by the ILAE as “a disorder characterized by enduring predisposition to generate epileptic seizures” [77]. In addition to structural and genetic epilepsies, seizures occurring due to a brain insult secondary to a congenital cytomegalovirus infection or other congenital infections are also considered remote symptomatic [4].

**C. Acute symptomatic seizures initially stopping within a few days or weeks, but eventually evolving after a latent period of variable duration in post-neonatal epilepsy.** About 18–33 % of survivors from neonatal seizures present unprovoked, remote symptomatic seizures, most of them within the first year of life [48,49,78,79]. Usually, unprovoked epileptic seizures in these children coincide with other significant disabilities such as cerebral palsy and cognitive impairment [19,80]. In conditions such as perinatal arterial ischemic stroke, the risk of developing post-neonatal epilepsy is rather high, with a latency of over a decade from the acute brain insult to the post-neonatal epilepsy [81]. In children with perinatal arterial ischemic stroke, the incidence of active epilepsy during the first decade of life is 54 % for those with a history of neonatal seizures, and neonatal seizures themselves have been acknowledged as the only independent predictor of remote seizures in this population [82].

**D. Acute symptomatic seizures that never stop, but directly evolve to post-neonatal epilepsy.** In these neonates, the acute aetiology has induced a particularly severe brain injury resulting in unprovoked seizures in close temporal proximity with the acute seizure onset, without a latent (seizure-free) period. In this scenario, the severe acute brain injury gives rise to impaired plasticity due to a significant rearrangement of neuronal networks in early developmental stages [83], so that the temporal

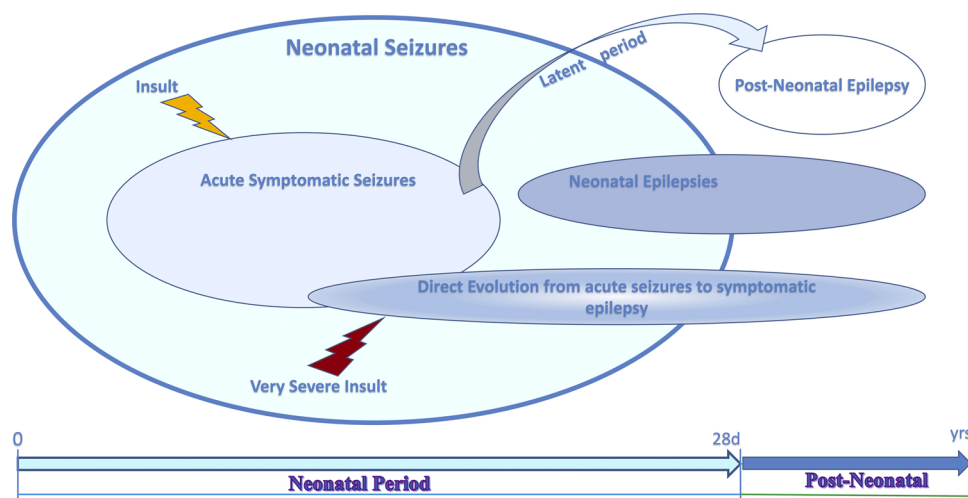


Fig. 1. Different clinical scenarios involving seizures in the neonatal period and their distinct post-neonatal evolution.

distinction between acute-stage seizures and remote ones is not clearly discernible. This last clinical scenario is rare, but may be encountered more often in (1) infectious encephalitis [84], (2) severe hypoxic ischemic encephalopathy (HIE) [85,86], and (3) neonatal hypoglycaemia [87]. It should, however, be noted that all three aetiologies may under certain circumstances potentially result in scenarios A and C, i.e. in acute symptomatic seizures that are either self-limiting or initially stop and later evolve into post-neonatal epilepsy after a latent period.

### 6.1. Examples of specific etiologies

#### 6.1.1. Viral encephalitis, HIE and hypoglycemia

Viral encephalitis is a common aetiology of seizures in all age groups, including neonates, and herpes simplex is the most common cause of sporadic encephalitis [84,88]. The estimated incidence of herpes encephalitis is 1/250 000–500 000 per year, concerning children and adolescents in one-third of cases, with a particularly high risk for severe neurological sequelae in very young children [89]. The necrotizing impact of the herpes simplex virus results in cortical scars that give rise to post-infectious epilepsy following encephalitis arises from regions with that are usually well-discernible in MRI [89]. Over 90 % of herpes encephalitis cases are linked to HSV-1 [90]. In HSV-1 encephalitis, brain damage can be widespread and severe, usually involving the frontal and temporal lobes as well as the insular cortex [89], and seizures occur in more than half of patients [91,92], with a significant seizure burden already at an early stage. Remote unprovoked seizures occur in 42–60 % of patients after HSV-1 encephalitis and are often intractable [93]. The processes of epileptogenesis involved in the generation of acute and remote seizures have not been fully understood so far [94–96]. Experimental studies in encephalitis-induced epilepsy have documented an activation of Toll-like receptors as a result of a brain affection by neurotropic viruses, although further studies will be needed to further clarify the mechanisms underlying epileptogenesis in these patients [97].

#### 6.1.2. Viral encephalitis, HIE and hypoglycemia

In severe HIE, acute seizures themselves may augment injury to the developing brain additional to that caused by the underlying aetiology [3,96,98], eventually evolving into structural epilepsy, with a high propensity for seizure recurrence. HIE represents the most important aetiology of neonatal seizures [47] and is responsible for 15–20 % of neonatal mortality as well as for major disabilities in the survivors, including epilepsy in 9–33 % [99]. Neonates with seizures in the context of HIE have a higher seizure burden, directly related to the severity of brain injury [83,100]. Those with a more severe brain injury, particularly those with involvement of the basal ganglia or watershed areas, have a higher risk of post-neonatal epilepsy [101,102]. The exact mechanisms of epileptogenicity are yet not completely understood but these may be partly related to a synaptic reorganization as a result of the neuronal injury [103,104] that culminates in particularly hyper-excitable cortical-brainstem neuronal networks, potentially modulated by basal ganglia disinhibition [105]. These changes lead to the occurrence of unprovoked, recurrent seizures, usually after a seizure-free latent period, as evidenced in clinical and experimental studies [86,106,107]. However, in particularly severe cases, this latent period may not be present, and acute symptomatic seizures may be directly followed by recurrent unprovoked seizures without evidence of a seizure-free period [106,108].

#### 6.1.3. Hypoglycemia

Neonates with HIE are at increased risk of depleting their energy stores and developing hypoglycaemia [109] that, in turn, has been acknowledged as an independent predictor of mortality, seizures, and severity of encephalopathy in HIE [110–113]. Irrespective of HIE, hypoglycaemia is a common issue in neonates, presenting in one third of those with neonatal encephalopathy [110,111]. In addition to visual

impairment [114], and cognitive deficits [115,116], neonatal hypoglycaemia has been associated with focal epilepsy [117,118]. In fact, several studies have demonstrated an occipital pattern of brain injury [73,114], with haemorrhagic lesions in the acute stage giving way to gliosis and atrophy in later stages [118] that, eventually give rise to posterior cortex epilepsies [119]. Occipital lobe epilepsies secondary to neonatal hypoglycaemia are refractory to treatment and carry a high risk of status epilepticus in the first years of life, even though some cases may enter remission in late childhood and adolescence [117]. HIE in term infants may also lead to posterior cortex epilepsy, adding to the complexity of differential diagnostics, particularly since HIE and hypoglycaemia may coexist, adding to the brain injury caused by each of the two conditions alone [120].

## 7. Epileptogenesis in the developing brain

The notion that neonatal seizures beget seizures is of paramount importance for seizure management in neonates, although the precise mechanisms of secondary epileptogenesis in the neonatal brain have not been conclusively clarified [121–123]. Experimental evidence supports that neonatal seizures lead to an increased susceptibility to seizures later in life [124]. Neonatal seizures in animal models, particularly when recurrent or prolonged, have been shown to augment seizure susceptibility depending on the age at insult [125] and on pre-existing brain damage, i.e. in the context of HIE [126]. The processes of secondary epileptogenesis are complex and can include loss of GABAergic interneurons, a shift back from the expression of the chloride exporter KCC2 to the chloride importer NKCC1, neuroinflammation with microglial activation and astrogliosis, and alterations in various signalling pathways, including the Janus kinase/signal transducer and activator of transcription (JAK/STAT), the mammalian target of rapamycin complex (mTORC), the BDNF/tyrosine receptor kinase B (trkB)/phospholipase Cc1 (PLCc1), and the IL-1R1/Toll-like receptor 4 (TLR4) pathways [97, 127–131]. On the other hand, clinical evidence supports that neonatal seizures, particularly when recurrent or prolonged, increase the risk for postneonatal epilepsy [132], whereas their effect is linked to the specific stage in brain development, with preterm neonates at higher risk [133].

The distinction between the clinical scenarios C and D, i.e. of secondary epileptogenesis with or without a latent period following the acute symptomatic seizures, is supported by both extensive experimental data in neonatal animal models and growing clinical evidence. Between the acute symptomatic seizures and the onset of recurrent unprovoked seizures [107], a latent period of further molecular and structural changes occurs, ultimately rendering the brain hyperexcitable and able to chronically generate seizures. Several types of brain insults occurring in the perinatal period, including stroke, severe HIE and cerebral infections, can promote such processes. Whether the cascades of molecular, structural and cellular mechanisms involved in secondary epileptogenesis differ according to the distinct transient epileptogenic insults and to what extent is yet unclear. However, different aetiologies seem to share common pathways [97]. The duration of the latent period can vary widely in both human and experimental models, ranging from days to months or years, possibly depending on the severity or nature of the process [127,128,134].

Interestingly, the universality of the concept of a “latent period” has been called into question and the presence of a latent period should no longer be considered a necessary prerequisite for or a global precursor of secondary epileptogenesis. Recent data both from animal models and from scalp and invasive EEG recordings in intensive care patients with brain injury suggest that subclinical and clinical seizures beginning during the acute phase of brain injury continue without significant interruption into the chronic epilepsy phase [134].

Although the precise mechanisms of epileptogenesis is yet unknown, it may be hypothesized that initial focal subclinical discharges in the context of a minimally injured brain may face inhibition to seizure spread that is bound to delay the appearance of clinical seizures and lead



to the clinical scenario C, with unprovoked seizures following a latent period after acute symptomatic seizures. However, if the initial damage is more severe and affects key brain structures such as the thalamus and basal ganglia [101,102], even the earliest focal discharges will be able to spread and produce clinical seizures [135]. In this light, the latent period corresponds to a process towards a gradually decreasing seizure threshold, as in kindling models, that leads to the recruitment of further brain areas along the maturation of epileptic networks [136,137]. The duration of this process is bound to vary according to the age of the patient as well as to the localization and severity of brain injury. However, despite recent advances in related research fields, the appreciation of the aetiology-specific progress of epileptogenicity remains an enigma [127].

## 8. Clinical management and prognosis

Current evidence supports the need for an early differential diagnosis between an acute symptomatic seizure and an unprovoked seizure, as this has significant implications in guiding patient management, counselling and prognostication, since it is associated with differences in clinical evolution.

Despite a mere 50–64 % response rate over the first 48 h after seizure onset in neonates [138,139], phenobarbital is still the drug of first choice for the management of acute symptomatic neonatal seizures [140], due to an older randomized controlled trial comparing phenobarbital to phenytoin [138] and a more recent randomized controlled trial comparing phenobarbital to levetiracetam [139] as well as due to the clinical experience accumulated over the last decades [141]. On the other hand, several anti-seizure medications, such as levetiracetam [21, 142,143] and topiramate [144], have emerged as viable alternatives with the potential to address age-specific mechanisms and challenges, whereas other anti-seizure drugs such as lidocaine and bumetanide are still under scrutiny due to cardiotoxicity [145–147] and ototoxicity [148,149] concerns.

Most clinical studies have been performed in the context of acute symptomatic seizures and rarely in remote symptomatic epilepsies, whereas for some genetic epilepsies, evidence supporting the use of more tailored pharmacological approaches has only recently become available [150–154]. In benign familial neonatal epilepsy, associated in >80 % of patients with mutations in KCNQ2 or KCNQ3, which regulate a potassium current, early diagnosis and treatment with oral carbamazepine is the key for rapidly attaining seizure freedom and normal cognitive development [150]. In the same line, patients with SCN1A mutations and early epilepsy onset in the first weeks of life may profit from treatment with sodium channel blockers, whereas other anti-seizure drugs are less effective [154]. Interestingly, this favourable response to sodium channel blockers clinically has been linked to gain-of-function mutations.

Clinical observations suggest that neonatal seizures usually abate after a few days, independent of therapeutic intervention [155], allowing withdrawal of antiseizure medications before discharge [156], although neither specific guidelines nor uniform duration treatment strategy yet exist [157]. Furthermore, there is no evidence that a protracted treatment can have a role in preventing the risk of recurrent unprovoked seizures later in life, as reportedly occurring in 18–25 % of cases [80]. On the contrary, there is evidence that prolonged treatment with phenobarbital may have deleterious effects on the developing brain [158–160].

At present, while we are able to correctly identify neonates at high risk for epilepsy and for an unfavourable outcome [132,161,162], we still do not have the therapeutic tools necessary to prevent the development of epilepsy following acute symptomatic seizures, as early prophylaxis with high doses of phenobarbital does not suffice to avert later seizure occurrence [163]. On the other hand, the increasingly available genetic testing for neonates with seizures together with a growing body of evidence regarding the optimal pharmacologic

treatment of genetic epilepsies may offer a window of opportunity for these particular subgroup of neonates [164,165].

## 9. Future strategies

Numerous potential lines of research arise from the topics addressed in this review. Does structural brain damage, as in cerebral haemorrhage, represent an epiphenomenon of an underlying genetic cause or does it actually contribute to secondary epileptogenesis [94]? Do electrographic seizures and periodic epileptic discharges documented in EEG during the acute brain insult predict later epilepsy? What is the role of high-frequency oscillations (HFO) in predicting epileptogenesis following brain injury in humans [166–169]? Will these arise as potent predictors of post-insult epilepsy, as demonstrated in animal models [170,171]? Will we succeed in designing antiepileptogenic drugs [107] and in reducing the severity of acute brain injury so as to avert its detrimental impact on the developing brain [127]? Clinical studies have an important role in further identifying the electroclinical and neuroimaging features that are associated with different temporal patterns of evolution from acute symptomatic seizures to later epilepsy. Advances in pattern recognition are expected to not only improve our theoretical understanding regarding this evolution, but also to facilitate the accurate classification and therefore the optimal management of neonatal seizures in the future.

## Declaration of Competing Interest

We the undersigned declare that the manuscript “The Conundrum of Neonatal Seizures: Acute Symptomatic, Remote Symptomatic, Provoked, Unprovoked Seizures, evolving to Post-neonatal Epilepsies, and Neonatal Onset Epilepsies” is original, has not been published before and is not currently being considered for publication elsewhere.

We confirm that all authors have participated in (a) conception and design; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We understand that the Corresponding Author is the sole contact for the Editorial process. She is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript

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