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FULL-LENGTH ORIGINAL RESEARCH

Neonatal presentation of genetic epilepsies: Early differentiation from acute provoked seizures

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Abstract

Objective: Although most seizures in neonates are due to acute brain injury, some represent the first sign of neonatal onset genetic epilepsies. Delay in recognition and lack of expert assessment of neonates with epilepsy may result in worse developmental outcomes. As in older children and adults, seizure semiology in neonates is an essential determinant in diagnosis. We aimed to establish whether seizure type at presentation in neonates can suggest a genetic etiology.

Methods: We retrospectively analyzed the clinical and electroencephalographic (EEG) characteristics of seizures in neonates admitted in two Level IV neonatal intensive care units, diagnosed with genetic epilepsy, for whom a video-EEG recording at presentation was available for review, and compared them on a 1:2 ratio with neonates with seizures due to stroke or hypoxic–ischemic encephalopathy.

Results: Twenty neonates with genetic epilepsy were identified and compared to 40 neonates with acute provoked seizures. Genetic epilepsies were associated with pathogenic variants in *KCNQ2* ($n = 12$), *KCNQ3* ($n = 2$), *SCN2A* ($n = 2$), *KCNT1* ($n = 1$), *PRRT2* ($n = 1$), and *BRAT1* ($n = 2$). All neonates with genetic epilepsy had seizures with clinical correlates that were either tonic (18/20) or myoclonic (2/20). In contrast, 17 of 40 (42%) neonates with acute provoked seizures had electrographic only seizures, and the majority of the remainder had clonic seizures. Time to first seizure was longer in neonates with genetic epilepsies (median = 60 h of life) compared to neonates with acute provoked seizures (median = 15 h of life, $p < .001$). Sodium channel-blocking antiseizure medications were effective in 13 of 14 (92%) neonates with tonic seizures who were trialed at onset or during the course of the epilepsy.

Significance: Seizure semiology is an easily accessible sign of genetic epilepsies in neonates. Early identification of the seizure type can prompt appropriate workup and treatment. Tonic seizures are associated with channelopathies and are often controlled by sodium channel-blocking antiseizure medications.

KEYWORDS

epilepsy, neonates, semiology, tonic, video-EEG

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1 | INTRODUCTION

Seizures are frequent in the neonatal period, affecting two per 1000 neonates.[1] Whereas most arise in the setting of acute brain injury, more than 10% of seizures in neonates reflect the onset of epilepsy.[2,3] Seizures resulting from neonatal onset epilepsies must be addressed differently from acute provoked seizures.[4,5] However, whereas fetal and postnatal magnetic resonance imaging (MRI) can easily detect structural brain malformations, the early diagnosis of genetic MRI-negative epilepsies is challenging. Genetic neonatal epilepsies are frequently associated with significant cognitive and behavioral morbidity.[6,7] For some genetic epilepsies, seizures respond particularly well to select agents, contrasting with the nonspecific approach traditionally used in the neonatal intensive care unit (ICU).[8] Early effective treatment could mitigate the effects of seizures on the developing brain, but this entails recognizing seizures and diagnosing epilepsy when it presents in the nursery.

Over the past decade, advances in both electroencephalographic (EEG) monitoring and genetic testing have provided clinicians with new, fast, and reliable diagnostic tools.[5] Identifying seizures and interpreting seizure type is challenging in adults[9] and children,[10] and even more so in neonates.[11,12] Nevertheless, a systematic review of the literature[13] suggests that seizure semiology in neonates may have diagnostic value with respect to etiology and thus implications for management.

The high yield of targeted exome analysis in neonates with genetic epilepsies[2,14] supports early genetic testing in infants with certain seizure phenotypes,[15] thus providing prognostic and genetic information for family planning and patient care and averting further unnecessary diagnostic testing. As the majority of neonates have acute provoked seizures, those with genetic epilepsies run the risk of being treated as such with medications that are ineffective, missing the window of opportunity for early targeted intervention. This can be prevented if providers have the clinical skill set to identify neonates with genetic epilepsy as different. Even when genetic testing returns a putative finding, confirmation of the epilepsy diagnosis with accurate phenotypic data is essential.[16]

In this study, we analyzed the video-EEGs (vEEGs) of neonates with seizures recorded at seizure onset, to describe the early semiology of seizure in neonates with genetic epilepsies and compare it with the semiology in neonates with acute provoked seizures.

Key Points

- As in older children, seizure semiology in neonates may point toward etiology; early recognition has diagnostic and therapeutic implications
- Many neonates with genetic epilepsy present with tonic seizures characterized by asymmetric tonic posturing, associated with apnea and desaturation
- In contrast, seizure semiology in neonates with acute provoked seizures is mostly clonic or electrographic only
- Tonic seizures are seen in channelopathies, most often fail to respond to phenobarbital, and promptly respond to oral carbamazepine

2 | MATERIALS AND METHODS

This study was approved by the Committee on Human Research at University of California, San Francisco (UCSF) and the Ethical Committee at Saint-Luc University Hospital, Catholic University of Louvain, and a waiver for informed consent was granted for this study.

2.1 | Population

Neonates with genetic epilepsies were identified by a systematic review of all neonates with 44 weeks or more of corrected gestation who received EEG monitoring and had a diagnosis of seizure in two Level IV neonatal ICUs (UCSF Benioff Children's Hospital, San Francisco, California, USA, and Saint-Luc University Hospital, Brussels, Belgium). Neonates for whom vEEG recordings were available for review were included. A subset of patients has been previously published.[2,17]

Genetic epilepsy was defined as a condition resulting directly from a known "pathogenic" or "likely pathogenic" genetic variant in which seizures are a core symptom of the disorder.[18] Genetic testing was performed on a clinical basis. Counseling and consent for genetic testing were conducted by the treating clinicians, and the clinical result reports were evaluated by the investigators. Variants were identified on either epilepsy targeted panels or whole exome sequencing. Single nucleotide polymorphism arrays or comprehensive genomic hybridization arrays were performed to search for copy number variation. The variants detected were queried against the Exome Variant Server database (evs.gs.washington.edu) to determine their prevalence in large control populations. PolyPhen-2 software (genetics.bwh.harvard.edu/pph2) was used to determine in silico likelihood of pathogenicity. Clinical significance of variants and inheritance patterns were queried using the ClinVar (ncbi.nlm.nih.gov/clinvar) and OMIM (ncbi.nlm.nih.gov/omim) databases.[19]

Subsequently, this group of neonates with genetic epilepsies was compared to consecutive neonates with acute provoked seizures due to either hypoxic–ischemic

encephalopathy (HIE) or stroke, the most common etiologies of seizures in this age group, in whom vEEG was recorded between January 2017 and December 2019, who were discharged seizure-free and without a diagnosis of epilepsy. Neonates who were paralyzed and neonates for whom video of seizures was not available for review were excluded. Based on effect size calculation, assuming that 10% of neonates with acute provoked seizure would have tonic seizures, including 20 neonates with genetic epilepsies and 40 with acute provoked seizures would allow us to detect a statistically significant difference between acute provoked seizures and genetic epilepsies, with two-sided alpha error set at .05 and 90% power if the difference in proportion was greater than 50%.

2.2 | vEEG analysis

vEEG recording was promptly initiated in neonates with encephalopathy and/or clinical events suspicious for seizures and continued until at least 24 h after the last seizure.[20] In addition, amplitude-integrated EEG (aEEG) was displayed at the bedside for real time evaluation by the neonatology team. Neonates with HIE were monitored upon admission during the whole duration of therapeutic hypothermia and through rewarming. vEEG recordings were analyzed by an experienced neonatal neurophysiologist (M.R.C.) and a neonatologist with expertise in neonatal EEG (M.-C.C.) for the purpose of the study. Clinical seizures without EEG correlate were not considered.

Seizure semiology was classified according to the new International League Against Epilepsy (ILAE) classification[21] as (1) clonic, (2) tonic, (3) sequential, (4) myoclonic, and (5) electrographic only. Seizure with an initial well-defined tonic phase followed by clonic or myoclonic jerks was classified as tonic. Tonic seizures were further classified as either tonic only or tonic sequential (initial tonic phase followed by either clonic or myoclonic jerks).

2.3 | Data analysis and statistical methods

Demographic data were collected from the electronic health record and managed using REDcap electronic data capture tools hosted at UCSF Benioff Children's Hospital.[22] Univariate statistical analyses were performed using the *t*-test or Wilcoxon rank sum (Mann–Whitney *U*) test for continuous variables and the Fisher exact test for categorical variables.

3 | RESULTS

Twenty patients with genetic epilepsies developed seizure at less than 44 weeks of corrected gestational age, had vEEG recording available for review, and were analyzed. We compared them with 40 term neonates with acute provoked seizures, 14 (35%) due to stroke and 26 (65%) due to HIE.

The demographics and seizure characteristics of neonates are presented in Table 1. vEEGs of seizures recorded before the administration of any antiseizure medication (ASM) was available in eight of 20 (40%) neonates with genetic epilepsies and 35 of 40 (87%) neonates with acute provoked seizures.

The seizure type in the 40 neonates with acute provoked seizures was mostly clonic or electrographic only, as 22 of 40 infants (55%) had at least one clonic seizure. Clonic seizures were more common in neonates with stroke (12/14, 86%) than with HIE (10/26, 38%, $p = .007$). Seventeen of 40 (42%) neonates had electrographic seizures only (HIE, 15/26, 58% vs. stroke, 2/14, 14%; $p = .017$). Electrographic seizures started 30 s or more before the onset of the clinical manifestation in 12 of 22 (55%) neonates with clonic seizures. The median time between electrographic onset and clinical onset in neonates with clonic seizures was 33 s (interquartile range [IQR] = 15–110 s).

In contrast, most infants with genetic epilepsies presented with tonic seizures (Figure 1), and all infants with tonic seizures showed clinical signs at the onset of the electrographic seizure. Eighteen of 20 (90%) neonates with genetic epilepsies had seizures characterized by an initial tonic phase with asymmetric tonic posturing. In 11 of them (61%), the tonic phase was followed by unilateral or bilateral clonic jerk representing sequential seizures. The remaining two infants with genetic epilepsies, both with *BRAT1* pathogenic variants, had myoclonic seizures. The tonic phase was followed by clonic jerks of the extremities in 11 of 18 (61%) patients with tonic seizures. The detailed clinical presentation of infants with genetic epilepsies is presented in Table 2. All neonates with genetic epilepsies had a clinical component associated with their seizures prior to treatment, and most continued to have clinical features after treatment initiation. Table 3 describes the distinct genetic pathogenic variants identified in each patient.

Seizure duration in neonates with acute provoked seizures tended to be longer (median = 268 s, IQR = 120–622 s) than in neonates with genetic epilepsies (median = 66 s, IQR = 38–103 s; $p < .001$). Furthermore, profound and prolonged background depression following the seizure was seen in 14 of 15 (93%) infants with variants in *KCNQ2*, *KCNQ3*, and *SCN2A*, independent of the duration of the seizure and the severity of the disease. This profound attenuation was longer than the seizure itself in 13 of 14 (93%) patients (Table 2). This background depression was not seen in infants with acute provoked seizures even after prolonged seizures, nor in those with *PRRT2*, *KCNT1*, or *BRAT1* pathogenic variants.

Seizure onset was before 48 h of life in eight of 20 (40%) infants with genetic epilepsies compared to 38 of 40 (95%) of infants with acute provoked seizures ($p < .001$). Only two

TABLE 1 Characteristics of neonates with genetic epilepsies and acute provoked seizures

	Genetic epilepsies, $n = 20$	Acute provoked seizures, $n = 40$	p
Demographics			
Male	10 (50%)	15 (38%)	.35
Gestational age, weeks	38.5 (38–40)	40 (39–41)	<.001
Birthweight, kg	3.3 (2.7–3.6)	3.2 (3.0–3.6)	.60
Apgar score, 5 min	9 (9–9)	5 (2–7)	<.001
Family history of neonatal seizure	9 (45%)	1 (3.3%)	<.001
Seizures			
Age at seizure onset, h	60 (26–96)	15 (10–22)	<.001
Treated with ≥2 ASMs	16 (80%)	13 (32%)	.001
All seizures were clinical	11 (55%)	4 (10%)	<.001
All seizures were subclinical	0 (0%)	17 (42%)	<.001
1 or more clonic seizure	3 (15%)	22 (55%)	.005
1 or more tonic seizure	18 (90%)	0 (0%)	<.001
1 or more myoclonic seizure	2 (10%)	1 (3%)	.44

All data are provided in *n* (%) or median (Interquartile range).

Abbreviation: ASM, antiseizure medication.

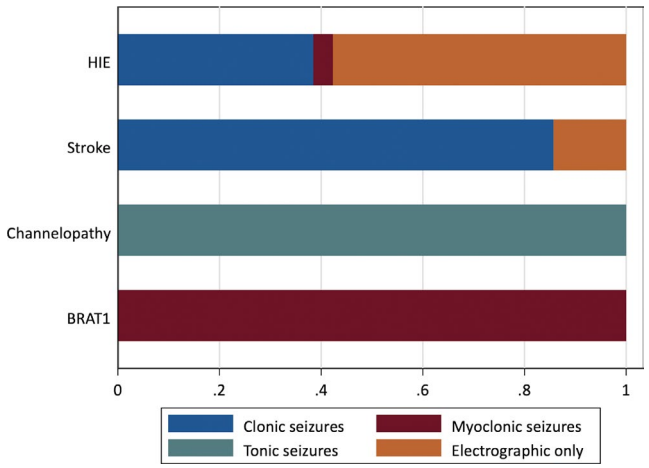


FIGURE 1 Seizure semiology at onset based on etiology. HIE, hypoxic–ischemic encephalopathy

neonates with acute provoked seizures had seizure onset after the first 48 h of life. One had a severely and diffusely depressed EEG background with seizure onset after rewarming, whereas the other had a single isolated 3-min clonic seizure at 64 h of life during therapeutic hypothermia, which went untreated. The patient was monitored for an additional 48 h, and seizures did not recur. Among neonates with genetic epilepsies, 18 of 20 (90%) had a confirmed channelopathy. Eight of 18 (44%) had seizure onset in the first 36 h of life, and among them, only one reached age-appropriate milestones at 3 months of life. Among the remaining 10 with seizure onset at or after 2 days of life, nine (90%) had a normal early neurodevelopment outcome at 3 months of age. The patients with *BRAT1* pathogenic variants had seizure onset after 2 weeks of life. Details regarding age at seizure onset according to etiology are provided in Figure 2. All but one neonate with genetic epilepsy and normal neurological examination at 3 months had a positive family history of neonatal seizures.

All infants with acute provoked seizures and 16 of 20 infants with epilepsy underwent MRI within 1 week from the onset of symptoms. Four infants with epilepsy and positive family history suggestive of self-limited familial neonatal epilepsy only underwent head ultrasound (Table 2).

In terms of treatment, five of 40 (13%) neonates with acute provoked seizures either were not treated or responded to a single administration of benzodiazepines. Of the remaining 35 neonates who received ASMs, 20 (57%) responded to phenobarbital loads of 20–40 mg/kg, one (3%) responded to a fosphenytoin load of 20 mg/kg, and one (3%) to levetiracetam 50 mg/kg as a first-line ASM. Among the 13 of 40 (33%) who required more than one ASM, all received both phenobarbital and phenytoin/fosphenytoin, and one also received levetiracetam and a midazolam infusion. Among the neonates with genetic epilepsies, 18 of 20 (90%) had tonic seizures, all associated with a channelopathy. Fourteen of 18 (78%) received a phenobarbital load as the first-line agent, which was ineffective in 13 of 14 (93%). Four of 18 (22%) received carbamazepine/oxcarbazepine initially and were seizure-free. Ten of 18 (78%) received carbamazepine/oxcarbazepine after failure of one to six other ASMs, and nine of them were seizure-free afterward. In particular, all neonates with *KCNQ2/3*-related epilepsies who were trialed on carbamazepine/oxcarbazepine responded with seizure freedom. Of note, eight of 14 (57%) infants received carbamazepine based on the electroclinical presentation, before the results

of genetic testing were available. The four patients who were not trialed on carbamazepine/oxcarbazepine required multiple ASMs to achieve seizure freedom.

4 | DISCUSSION

This observational double-cohort study across two centers aims to provide epileptologists, neurologists, and neonatologists with an accurate and practical approach to seizures in neonates and to allow the rapid discrimination of neonates with genetic epilepsies from the larger group of neonates with acute provoked seizures (Figure 3). Epilepsy is complex, with multiple potential clinical manifestations, etiologies, treatments, and outcomes. In the past few years, there has been significant progress in the understanding of seizures and epilepsy in neonates, which is reflected in evolving terminology.[21]

Accurate interpretation of seizure semiology in adults and children guides the workup and allows for tailored treatment. Many childhood epilepsy syndromes have highly characteristic semiological features that epileptologists and neurologists have learned to recognize. We believe that the same approach is urgently needed for neonates. Our study shows that the seizure semiology at onset significantly correlates with etiology. Concordant with the recent study by Santarone et al.,[23] we showed that focal clonic seizures are strongly suggestive of acute provoked seizures, in particular stroke. Also consistent with previous reports,[3] we found a high rate of electrographic only seizures in critically ill neonates with acute provoked seizures. Nearly half of neonates with acute provoked seizures never had a clinical correlate to their seizure. This finding highlights the need for continuous vEEG monitoring in high-risk neonates.

In this cohort, all neonates with genetic epilepsies had seizures with clinical correlates prior to ASMs, and more than two thirds retained a clinical correlate throughout their course. For some of them, the clinical manifestations were still present after repeated loads of phenobarbital.

As suggested by a recent systematic review,[13] we found that most neonates with genetic epilepsies present with tonic seizures. An exception was noted in neonates with *BRAT1*-related encephalopathy whose seizures are myoclonic.[24,25] Importantly, neonates with inborn errors of metabolism also tend to present with myoclonic seizures. Recognizing these conditions early is essential due to implications for specific therapies.[8]

Minimizing delays in seizure control may contribute to better developmental outcomes.[26] In the past decade, the implementation of continuous vEEG monitoring in the neonatal ICU has helped to reduce the gap between seizure onset and treatment administration, especially for those neonates with HIE whose seizures are mainly electrographic only.[27] Nevertheless, the correct diagnosis and appropriate treatment for neonates with genetic epilepsies remain challenging. Historically, "neonatal seizures" were considered a single entity. Neonates still often receive a load of phenobarbital as first-line antiseizure treatment by protocol regardless of seizure type and etiology, even though concerted efforts are trying to distinguish acute provoked seizures from genetic epilepsies.[4] Consistent with recent studies,[28–30] we have shown that phenobarbital is generally ineffective in neonatal genetic epilepsies, as it resulted in persistence or early recurrence of seizures in eight of nine infants. The most recent ILAE position papers for classification of epilepsies[18,21] incorporate etiology along each stage of the classification. However, when it comes to neonates, we are a step behind, as the critical and clinically essential distinction between acute provoked seizures and seizures as a manifestation of genetic epilepsies is rarely made in the neonatal ICU.[4] Early recognition of infants with genetic epilepsies is essential, as some may obtain rapid seizure control with sodium channel blockers, including carbamazepine, which may limit the impact of seizures on the developing brain.[8] Although no ASM is approved for use in neonates, phenobarbital is widely used as a first-line treatment choice. Randomized controlled trials to study the efficacy of ASMs in neonates have been very limited,[8] and not stratified to evaluate efficacy in neonatal onset genetic epilepsies, reflecting a gap in knowledge. In our cohort, all but one neonate with tonic seizures who were trialed off-label on carbamazepine or oxcarbazepine as first-, second-, or third-line therapy ($n = 13$) responded with seizure freedom within hours. Our findings highlight the importance of correct interpretation of seizure semiology in neonates and the use of appropriate descriptive terminology. This emerging approach requires the elimination of the old monolithic notion of "neonatal seizures" as a single entity, and the acknowledgment that seizures in the nursery may be either acute provoked or the manifestation of neonatal epilepsies.[21] Those two conditions are different, and for each there are different etiologies, including rare or ultrarare disorders.

Although vEEG monitoring is the gold standard for diagnosing and classifying seizures in neonates, it may not be available, especially in the context of limited resources. Tonic seizures are easy to recognize at the bedside, as they are stereotyped with asymmetric tonic posturing and often prolonged enough to induce apnea and cyanosis. When witnessed or reviewed on video by experienced personnel, they may suggest a channelopathy, guide investigations, and justify a trial with oral carbamazepine.[8] The aEEG pattern of *KCNQ2*-related seizures is also pathognomonic,[31] reflecting quite nicely the pattern seen on the full EEG, and its observation may improve the recognition of these not so rare forms of genetic epilepsies.

For a diagnosis with severely limited lifespan, such as *BRAT1*-related encephalopathy, recognizing the clinical

TABLE 2 Clinical presentation, management, and outcome of the 20 neonates with genetic epilepsies

Case	Sex	Gene	Family history[a]	EEG background	Age at seizure onset	Seizure semiology	Seizure duration at onset and duration of background depression
1	F	*KCNQ2*	No	Lack of organization and physiologic features with almost-continuous multifocal epileptiform abnormalities intermixed with random asynchronous attenuations	72 HOL	Asymmetric tonic posturing, sometimes with paroxysmal bradycardia and desaturations; sometimes can have bilateral tonic posturing of upper and lower extremities	30 s followed by 90 s depression
2	M	*KCNQ2*	No	Multifocal epileptiform abnormalities intermixed with random attenuations	36 HOL	Asymmetric tonic posturing sometimes followed by unilateral or bilateral clonic jerks of upper and/or lower extremities	50 s followed by 60 s depression
3	F	*KCNQ2*	No	Multifocal epileptiform abnormalities intermixed with random attenuations	28 HOL	Ictal cry followed by asymmetric tonic posturing sometimes followed by clonic jerks	55 s followed by 90 s depression
4	F	*KCNQ2*	Yes	Occasional central interictal spikes and otherwise normal background	25 HOL	Asymmetric tonic posturing followed by clonic jerks	100 s followed by 120 s depression
5	M	*KCNQ2*	Yes	Normal	80 HOL	Asymmetric tonic posturing followed by clonic jerks	35 s followed by 190 s depression
6	F	*KCNQ2*	Yes	L>R centrotemporal sharp waves and otherwise normal background	77 HOL	Asymmetric tonic posturing followed by clonic jerks	65 s followed by 100 s depression
7	M	*KCNQ2*	No	Multifocal epileptiform abnormalities with random attenuation, alternating with periods of asynchronous and asymmetric burst-suppression	10 HOL	Asymmetric tonic posturing with desaturation and tachycardia	22 s followed by 180 s depression
8	F	*KCNQ2*	No	Multifocal epileptiform abnormalities intermixed with random attenuations	12 HOL	Asymmetric tonic posturing with desaturation	25 s followed by 50 s depression
9	M	*KCNQ2*	Yes	Normal	96 HOL	Focal tonic with apnea and desaturation	83 s followed by 90 s depression
10	F	*KCNQ2*	Yes	Central spikes and sharps on otherwise normal background	80 HOL	Focal tonic with apnea and desaturation followed clonic phase	60 s followed by 90 s depression
11	M	*KCNQ2*	No	Normal	48 HOL	Focal tonic, perioral cyanosis, desaturation 60%, followed by bilateral clonic jerks	60 s followed by 60 s depression
12	M	*KCNQ2* *TSC2*	No	Initially normal, then multifocal spikes with attenuations in the setting of multiple antiseizure medications	36 HOL	Focal asymmetric tonic with alternating laterality, perioral cyanosis, bilateral clonic jerk, tachycardia 220 bpm followed by marked bradycardia 60 bpm in the immediate postictal phase	110 s followed by 120 s depression

Seizure frequency[b]	Treatment	Imaging	Seizures at 3 months	Neuro exam at 3 months
35/h	PB, LEV, TPM, VGB, CLB, CZP, KD, B6, PLP, CBZ 20 mg/kg/day (effective)	MRI: mild hypomyelinization at 20 DOL and thin corpus callosum	Seizure-free on CBZ	No eye tracking, axial hypotonia and opisthotonos
1/h	PB, LEV, B6, CBZ 20 mg/kg/day (effective)	MRI: mild thinning of the corpus callosum	Seizure-free on CBZ	Eye tracking but axial hypotonia and irritability
1/h	PB, CBZ 15 mg/kg/day (effective)	MRI: normal	Seizure-free on CBZ	No eye tracking, axial hypotonia
3/day	PB, LEV, CBZ 10 mg/kg/day (effective)	MRI: normal	Seizure-free on CBZ	Normal
3/day	CBZ 10 mg/kg/day (effective)	HUS: normal	Seizure-free on CBZ	Normal
2/day	CBZ 10 mg/kg/day (effective)	HUS: normal	Seizure-free on CBZ	Normal
4/h	PB, LEV, CBZ 20 mg/kg/day (effective)	MRI: normal	Seizure-free on CBZ	Poor eye tracking, axial hypotonia
1/h	PB, LEV, LTG, VPA, KD, OXC 35 mg/kg/day (effective)	MRI: normal	Seizure-free on OXC	Poor eye tracking, axial hypotonia
3/day	PB, PHT, B6, LEV (partially effective 40 mg/kg/day)	MRI: normal	1–2 seizures/month on LEV	Normal
3/day	CBZ 15 mg/kg/day (effective)	HUS: normal	Seizure-free on CBZ	Normal
1–2/day	PB, B6, PHT 20 mg/kg/load (effective), LEV 20 mg/kg/day (effective)	MRI: normal	Seizure-free on PB and LEV	Normal
4–5/day	PB, PHT, LEV, B6, VGB, MDZ, CBZ 15 mg/kg/day (effective)	MRI: normal	Seizure-free on CBZ	Mild axial hypotonia

(Continues)

TABLE 2 (Continued)

Case	Sex	Gene	Family history[a]	EEG background	Age at seizure onset	Seizure semiology	Seizure duration at onset and duration of background depression
13	F	*KCNQ3*	Yes	Normal	5 DOL	Focal tonic with hyperextension of limbs, eyes and head deviation, desaturation followed by bilateral lower limbs clonus	120 s, no depression
14	F	*KCNQ3*	Yes	Normal	96 HOL	Asymmetric tonic posturing followed by clonic jerks	70 s followed by 130 s depression
15	M	*KCNT1*	No	Symmetric, theta-delta medium to low amplitude, lack of organization and physiological features, frequent multifocal epileptiform abnormalities intermixed with random attenuations	1 HOL	Asymmetric tonic, eye and head deviation, deviation of the angle of the mouth associated with apnea and desaturation	60 s, no depression
16	M	*PRRT2*	Yes	Normal	7 DOL	Asymmetric tonic posturing, at times associated with ipsilateral or contralateral eye deviation, oral automatism, and occasionally followed by hemiclonic jerking	90 s, no depression
17	F	*SCN2A*	No	Burst-suppression pattern or multifocal epileptiform abnormalities with a lack of normal named patterns in the setting of PB loads	3 HOL	Eye deviation, lip smacking/chewing movements, followed sometimes by tonic extension of the extremities, then a brief self-resolving desaturation	20 s followed by 30 s depression
18	M	*SCN2A*	Yes	Normal	48 HOL	Focal with initial hypertonia followed by hypotonia and cyanosis	110 s followed by 50 s depression
19	M	*BRAT1*	No	Bilateral frontal epileptiform abnormalities and otherwise normal background	17 DOL	Multifocal myoclonic seizures at presentation, focal clonic seizures involving face and limbs with alternating side appeared at 4 weeks of age	20 s
20	F	*BRAT1*	No	Frequent runs of rhythmic sharpened delta and multifocal sharp waves and otherwise normal background	23 DOL	Multifocal myoclonic seizures at presentation, multifocal clonic seizures appeared at 3 weeks of age	30 s, no depression

Abbreviations: B6, pyridoxine; B9, folic acid; CBD, cannabidiol; CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; DOL, days of life; EEG, electroencephalogram; F, female; FOS, fosphenytoin; HOL, hours of life; HUS, head ultrasounds; KD, ketogenic diet; L, left; LEV, levetiracetam; LTG, lamotrigine; M, male; MDZ, midazolam; MRI, magnetic resonance imaging; OXC, oxcarbazepine; P5P, pyridoxal-5-phosphate; PB, phenobarbital; PHT, phenytoin; PLP, pyridoxal phosphate; R, right; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide.

[a]Family history of neonatal seizures.

[b]Seizure frequency before effective treatment.

phenotype including erratic myoclonic seizures may help refocus the care, diminish the infant's suffering, and support familial bereavement, rather than pursuing futile, often painful, and ineffective efforts for extension of life.[32] *BRAT1* is not included in most targeted epilepsy panels, and identification of pathogenic variants in this gene requires whole exome

Seizure frequency[b]	Treatment	Imaging	Seizures at 3 months	Neuro exam at 3 months
1–2/day	PB, B6, LEV 20 mg/kg/day (partially effective), CBZ 11 mg/kg/day (effective)	MRI: focal diffusion anomalies in RBG	Seizure-free on CBZ	Normal
2/day	CBZ 10 mg/kg (effective)	HUS: normal	Seizure-free on CBZ	Normal
2/h	PB, TPM, CZP, PHT, B6, KD, LEV, CBD, potassium bromide	MRI: normal	Daily seizures on PB and potassium bromide	No eye tracking, axial hypotonia
5/h	PB, CBZ 10 mg/kg/day (effective)	MRI: normal	Seizure-free on CBZ	Normal
10/h	PB, LEV, B6, TPM, CLB (partially effective), CBZ 40 mg/kg/day (partially effective; weekly seizures)	MRI: normal	Weekly seizures on CBZ and CLB	No eye tracking, axial hypotonia, intermittent posturing
2–3/day	PB, VPA 30 mg/kg/day and VGB 100 mg/kg/day (partially effective)	MRI: normal	Seizure-free on VPA and VGB	Normal
10/day	LEV, CBZ, PHT, B6, PB, P5P, MDZ, ZNS, PHT, VPA	MRI: normal	Refractory before death	Diffuse hypertonia; no milestones reached, died at 66 DOL
5/h	CZP, B6, B9, PB, LEV, CLB, FOS, P5P, TPM, MDZ	MRI: microcephaly	Refractory before death	Diffuse hypertonia; no milestones reached, death at 69 DOL

sequencing, as the associated lethal condition, an autosomal recessive disorder, is ultrarare and has been recognized only recently.[24] Informing geneticists of the clinical phenotype may help to target variants in candidate genes, accelerate the diagnosis, and provide the family with essential information for reproductive counseling.

TABLE 3 Details of diagnostic genetic results for neonates with genetic epilepsy

Case	Gene	UniProtKB identifier	NCBI identifier	Coding sequence variant	Protein variant	Type	Zygosity	Origin	Clinical reports (ClinVar, OMIM)
1	*KCNQ2*	O43526	NM_172107.2	c.1734 G>C	p.M578I	Missense	Heterozygous	De novo	Reported rs796052655 (Numis et al. 2014)
2	*KCNQ2*	O43526	NM_172107.2	c.841 G>T	p.G281W	Missense	Heterozygous	De novo	Reported rs794727813 (Pisano et al. 2015)
3	*KCNQ2*	O43526	NM_172107.2	c.683 A>G	p.H228R	Missense	Heterozygous	De novo	Published (Benetou et al. 2019)
4	*KCNQ2*	O43526	NM_172107.2	c.619 C>T	p.R207W	Missense	Heterozygous	Unknown	Published (Dedeket et al. 2001, Blumkin et al. 2012)
5	*KCNQ2*	O43526	NM_172107.2	c.807 G>A	p.W269X	Nonsense	Heterozygous	Inherited	Published (Singh et al. 2003)
6	*KCNQ2*	O43526	NM_172107.2	c.807 G>A	p.W269X	Nonsense	Heterozygous	Inherited	Published (Singh et al. 2003)
7	*KCNQ2*	O43526	NM_172107.2	c.1749 G>C	p.K583N	Missense	Heterozygous	Unknown	Novel
8	*KCNQ2*	O43526	NM_172107.2	c.1088 A>G	p.Y363C	Missense	Heterozygous	Unknown	Published (Butler et al. 2017)
9	*KCNQ2*	O43526	NM_172107.2	c.1021 C>T	p.Q341*	Nonsense	Heterozygous	Inherited	Published (Gomis Perez et al. 2018)
10	*KCNQ2*	O43526	NM_172107.2	c.1021 C>T	p.Q341*	Nonsense	Heterozygous		Published (Inn-Chi Lee et al. 2019)
11	*KCNQ2*	O43526	NM_172107.2	c.1741 C>T	pR581*	Nonsense	Heterozygous	De novo	Reported RCV000678061.1
12	*KCNQ2*	O43526	NM_172107.2	c.388 G>A	p.E130K	Missense	Heterozygous	De novo	Reported RCV000203592.1
13	*KCNQ3*	O43525	NM_004519.3	c.1060 G>A	p.G354R	Missense	Heterozygous	Inherited	Reported rs796052680
14	*KCNQ3*	O43525	NM_004519.4	c.923 G>C	p.W308S	Missense	Heterozygous	Inherited	Reported rs1064794632
15	*KCNT1*	Q5JUK3	NM_020822.2	c.776 C>A	p.A259D	Missense	Heterozygous	De novo	Published (Numis et al. 2018)
16	*PRRT2*	Q7Z6L0	NM_001256442.1	c.649dupC	p.R217fs*8	Frameshift	Heterozygous	Inherited	Published (Scheffer et al. 2012)
17	*SCN2A*	Q99250	NM_021007.2	c.2713 A>G	p.K905E	Missense	Heterozygous	De novo	Reported rs886043250 (Butler et al. 2017)
18	*SCN2A*	Q99250	NM_021007.2	c.718 G>A	p.V261L	Missense	Heterozygous	Inherited	Reported rs1064795014
19	*BRAT1*	Q6PJG6	NM_001350626.1	c.638dup & c.2005 C>T	p.V214Gfs*189 & p.R669W	Missense	Compound heterozygous	Inherited	Novel
20	*BRAT1*	Q6PJG6	NM_001350626.1	c.1203_1204delTG & c.431-10_431-7delCCCTins TGGGTAGGG	p.C401X & IVS4-10_IVS4-7delCCCTins TGGGTAGGG	Nonsense	Compound heterozygous	Inherited	Reported rs773772842 & novel

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CNV, copy number variation; ESP, Exome Sequencing Project; N/A, not available; NCBI, National Center for Biotechnology Information; NGS, next generation sequencing; OMIM, Online Mendelian Inheritance in Man; VUS, variant of uncertain significance; WES, whole exome sequencing.

Our study shares limitations of retrospective studies, namely the potential for ascertainment bias. Although having neonates monitored with rigorous guidelines allowed us to compare all cases optimally, the number of included neonates with genetic epilepsies is relatively low. Genetic epilepsies are rare, and good quality vEEG monitoring at the onset of

Impact prediction (PolyPhen-2)	Minor allele frequency (ESP)	Mode of inheritance	Variant classification	CNV	Other comments	Diagnostic test
1	0	AD	Pathogenic	–	SCN1A c.3405 A>G (VUS maternally inherited) *TSC2* c.5095 G>A (VUS paternally inherited)	Targeted NGS gene panel
1	0	AD	Pathogenic	–	Compound heterozygous *RTTN* (c.1921A>G and c.3581A>G)	WES
1	0	AD	Likely pathogenic	–		Targeted NGS gene panel
1	0	AD	Pathogenic	–		Targeted NGS gene panel
NA	0	AD	Pathogenic	–		Targeted NGS gene panel
NA	0	AD	Pathogenic	–		Single gene
1	0	AD	Likely pathogenic	Normal		Targeted NGS gene panel
1	0	AD	Likely pathogenic	–		Targeted NGS gene panel
NA	0	AD	Pathogenic	Normal		Targeted NGS gene panel
NA	0	AD	Pathogenic	Normal		Single gene
NA	0	AD	Pathogenic	Normal		Targeted NGS gene panel
1	0	AD	Pathogenic	Normal	*TSC2* pathogenic variant mosaicism 2.4%	Targeted NGS gene panel followed by WES
1	0	AD	Likely pathogenic	Normal		Targeted NGS gene panel
.982	0	AD	Likely pathogenic	–		Targeted NGS gene panel
.630	0	AD	Pathogenic	Normal		WES
NA	0	AD	Pathogenic	Normal		WES
.998	0	AD	Pathogenic	Normal		(Single gene *KCNQ2/3*) WES
.999	0	AD	Pathogenic	Normal		Targeted NGS gene panel
NA	0	AR	Pathogenic/likely pathogenic	Normal		WES
NA	0	AR	Likely pathogenic/likely pathogenic	Normal		WES

symptoms is not always available. Whereas we have 13 patients with *KCNQ2*-related epilepsies, we have only one or two patients with other genetic etiologies, and our cohort does not encompass all the known genetic etiologies of neonatal epilepsy. Neonatal epilepsies include a complex and nuanced range of disorders, with an expected spectrum of

seizure types, treatment responses, and outcomes. Our data raise awareness on the importance of the recognition of the early clinical phenotype and are intended to motivate larger multicenter collaboration with detailed phenotyping extended to other etiologies of neonatal epilepsies, including brain malformations and epilepsies associated with inborn errors of metabolism.

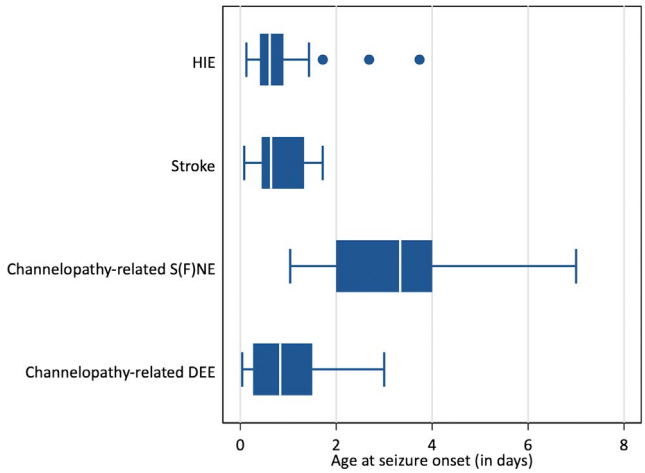
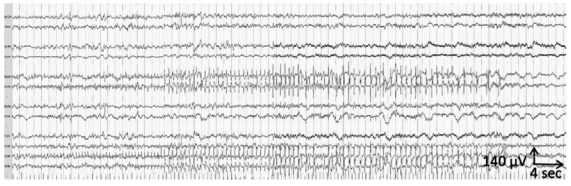
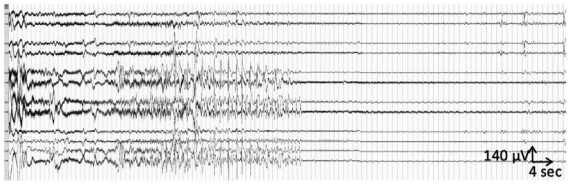
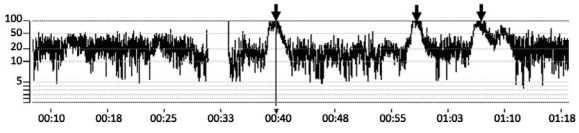
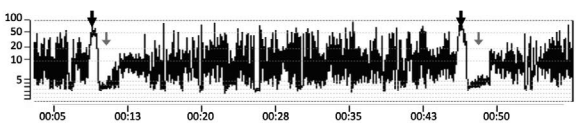


FIGURE 2 Age at first seizure according to etiology. DEE, developmental epileptic encephalopathy; HIE, hypoxic–ischemic encephalopathy; S(F)NE, self-limited (familial) neonatal epilepsy

5 | CONCLUSIONS

Infants with neonatal onset genetic epilepsies frequently remain undiagnosed until later in life, as the distinction between acute provoked seizures and epilepsy is seldom made in the neonatal ICU. We aimed to provide insight to help early discrimination of these different entities. Neonates with channelopathies, including *KCNQ2/3*-, *SCN2A*-, and *KCNT1*-related epilepsies, often have tonic or sequential seizures with a tonic component, a seizure type usually not observed in acute provoked seizures. Seizures associated with developmental and epileptic encephalopathies tend to arise in the first 48 h of life, at a time when acute provoked seizures are very common; later presentation and positive family history suggests a self-limited form. As neonatal seizures reach the mainstream,[4] and their precise characterization is recognized,[21] we should be able to raise the index of diagnostic suspicion and prioritize infants with rare conditions for targeted investigations. Prompt recognition of tonic seizures in the setting of normal imaging, especially in neonates with a positive family history, may inform diagnostic testing and allow for a trial with carbamazepine/oxcarbazepine in the neonatal ICU, while awaiting genetic testing confirmation, avoiding ineffective and potentially harmful medications. This approach can also reduce unnecessary diagnostic procedures and their associated costs, and early enrollment

	Acute provoked seizures	Neonatal onset epilepsies
Seizure	Duration: Often prolonged Semiology: Electrographic only or clonic (especially in stroke) Frequent delayed onset between electrographic seizure and clinical manifestations EEG: Focal, slowly evolving rhythm; no prolonged postictal depression	Duration: Mostly short (1-2 minutes) Semiology: Tonic, tonic sequential (myoclonic in *BRAT1*) Clinical manifestations seen at seizure onset EEG: Attenuation and fast activity, rapid spread; prolonged postictal depression
EEG		
aEEG		

	HIE	Acute ischemic stroke	Self-limited (Familial) Neonatal Epilepsy	Developmental Epileptic Encephalopathy
Interictal EEG	Abnormal	Variable	Normal (Peri-ictal epileptiform abnormalities)	Abnormal
Seizure onset	First 24-48 HOL	First 48 HOL	After 48 HOL	Variable
Family history	No	No	Often	Rare
Encephalopathy	Yes	No	No	Yes

FIGURE 3 Summary of the clinical and electroencephalographic (EEG) features in acute provoked seizures and neonatal onset epilepsies. Black arrows indicate seizures; grey arrows indicate postictal depression. EEGs: Gain,10 µV/mm; high-frequency filter, 70 Hz; paper speed, 15 mm/s. aEEG, amplitude-integrated EEG; HIE, hypoxic–ischemic encephalopathy; HOL, hours of life

in clinical research protocols to evaluate precision medicine therapies. Finally, a definite diagnosis allows families of neonates with rare genetic epilepsies and encephalopathies to receive personalized counseling and find support from others with the same conditions, even when separated by great distances.

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CONFLICT OF INTEREST

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