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Neonatal epilepsies: Clinical management

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A B S T R A C T

Whereas the majority of seizures in neonates are related to acute brain injury, a substantial minority are the first symptom of a neonatal-onset epilepsy, often linked to a pathogenic genetic variant. This defect may disrupt cortical development (e.g., lissencephaly, focal cortical dysplasia), lead to metabolic changes (e.g., pyridoxine-dependent epilepsy, sulfite oxidase deficiency) or lead to cortical dysfunction without metabolic or macroscopic structural changes (e.g., channelopathies, *STXBP1*). Historically, studies on treatment response and long-term consequences of neonatal seizures have lumped all etiologies together. However, etiology has been consistently shown to be the most important determinant of outcome. Here, we address the elements differentiating neonatal-onset epilepsies from acute symptomatic seizures. We review some common neonatal-onset epilepsies and emphasize how pathognomonic electro-clinical phenotypes such as the ones associated with *KCNQ2* or *KCNT1* gene mutation, when recognized early, can lead to targeted diagnostic testing and precision medicine treatment, enabling the possibility of improved outcome.

1. Introduction

Whereas most seizures in the neonatal period are due to acute brain injury, in a substantial proportion, seizures in the first days of life reflect the onset of epilepsy [1,2]. Historically, however, neonatal seizures have been studied by lumping all etiologies together. Over the last decade, our understanding of neonatal-onset epilepsies has greatly improved, thanks to progress in neuroimaging, metabolic and genetic testing. Newborn screening was the first step, enabling the diagnosis of severe conditions such as phenylketonuria or biotidinase deficiency, leading to early targeted treatment and improved outcome. Advances in genomic technologies have unveiled many pathologic genetic variants causing neurodevelopmental disorders including epilepsies [3,4]. In addition, the role of genetic testing as a guide for short- and long-term management with potential to improve outcome is expanding [5,6], leading to a new precision medicine approach.

Early recognition of the electro-clinical phenotype specific to each condition is essential for targeted treatment. The recommendations of the American Clinical Neurophysiology Society in 2011 to monitor all neonates at high risk for seizures with long-term video-electroencephalography (EEG) [7], as well as the development of brain-oriented neonatal intensive care units, has led to enhanced collaboration between neonatologists and neurologists, resulting for the first time in the delineation of electro-clinical phenotypes [5,8,9] based on etiology (Table 1). We are now able to move beyond the broad classification scheme outlined in the 1970s as Othahara syndrome or early myoclonic encephalopathy to more precise etiology-specific syndromes associated with distinct electro-clinical phenotypes (e.g., *KCNQ2*, *STXBP1*, or glycine encephalopathy).

2. Diagnostic approaches to neonatal epilepsies

In the acute setting, it is important to first rule out seizures that are due to acute brain injury, such as those related to hypoxic–ischemic encephalopathy (HIE), stroke, infection and transient metabolic disturbance. Yet, coexisting illness predisposing neonates with epilepsy to acute symptomatic seizures are not infrequent [1].

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Table 1
Distinctive features of various neonatal-onset epilepsies associated with single gene mutations.

Phenotype MIM number Transmission	Gene/ locus MIM number	Seizures	Interictal	Treatment	Outcome	Comments
Pyridoxine-dependent epilepsy #266100 AR	*ALDH7A1* 107323	Onset: in utero to first hours of life. Semiology: clonic seizure + myoclonic jerks +/− tonic seizure. Frequency: high, up to SE.	Encephalopathy. EEG: generalized bursts of 1−4 Hz sharp and slow activity, if untreated can progress into BS; rarely normal.	Pyridoxine (first dose in ICU) + lysine restricted diet + L-arginine supplements.	ID, motor and/or speech delay in up to 75%.	Treat pregnant women at risk. Some cases of late-onset seizure (up to 6 months of life).
Pyridoxamine 5-phosphate oxidase deficiency #610090 AR	*PNPO* 603287	Onset: in utero to first hours of life. Frequency: high, up to SE. Semiology: clonic seizure + myoclonic jerks +/− tonic seizure.	Encephalopathy. EEG: generalized bursts of 1-4 Hz sharp and slow activity, if untreated can progress into BS; rarely normal.	Pyridoxal phosphate (some may respond to pyridoxine).	From mostly normal to severe ID and death.	Prematurity is common. May mimic HIE.
Glycine encephalopathy #605899 AR	*GLDC* 238300 *AMC* *GCSH*	Onset: usually first day of life. Semiology: tonic or clonic seizures. Refractory.	Normal at birth, progressive encephalopathy in first hours up to coma. Myoclonus and hiccup is frequent. EEG: BS pattern, often asynchronous.	No effective treatment.	Apnea and early death; profound ID in survivors, except for rare transient forms.	MRI: callosal thinning, progressive cortical atrophy, and delayed myelination. Sometimes agenesis of corpus callosum and gyral malformations.
Sulfite oxidase deficiency #272300 AR	*SUOX* 606887	Onset: first hours to days of life. Semiology: poorly described. Sometimes myoclonic or tonic −clonic. Frequent and refractory.	Severe encephalopathy, tone abnormalities. EEG: BS pattern.	Dietary therapy might improve outcome in late-onset cases.	Profound ID, movement disorder and early death.	Late-onset milder forms exist. Clinical finding and MRI may mimic HIE.
Molybdenum cofactor deficiency #252150 AR	*MOCS1* 603707	Onset: first hours to days of life. Semiology: poorly described. Sometimes myoclonic or tonic-clonic. Frequent and refractory.	Encephalopathy, exaggerated startle reaction, axial hypotonia, limb hypertonia, and feeding difficulties.	Daily cyclic pyranopterin before seizure onset might improve outcome.	Profound ID, poor feeding and early death.	May also be due to *MOSC2* or *GPHN* gene.
SLC13A5-associated EE #615905 AR	*SLC13A5* 608305	Onset: first week of life (most in the first day of life). Semiology: focal seizure, chewing, clonic movements and desaturation. Refractory seizure leading to SE.	Good perinatal adaptation evolves to encephalopathy. EEG: normal/mildly discontinuous background initially.	Lidocaine, midazolam and ketogenic diet effective in some patients.	Severe to profound ID, frequent choreoathetosis, ataxia, dystonia.	MRI: punctuate white matter lesions that disappear by 6 months and lead to gliotic scarring.
Benign familial neonatal epilepsy (BFNE) #121200/#121201 AD	*KCNQ2* 602235 *KCNQ3* 602232	Onset: first days of life. Semiology: asymmetric tonic posturing shifting laterality +/− clonic movement +/− apnea and desaturations. Frequency: variable up to SE.	Normal clinical exam between seizures. EEG: normal background.	Carbamazepine/oxcarbazepine.	Normal development; epilepsy recurrence in up to 25%.	Distinctive pattern on aEEG with sudden rise of the lower and upper margin, followed by marked amplitude depression.
KCNQ2- EE #613720 AD	*KCNQ2* 602235	Onset: first days of life. Semiology: asymmetric tonic posturing shifting laterality +/− clonic movement +/− apnea and desaturations.	Encephalopathy. EEG: lack of organization and multifocal epileptiform abnormalities.	Carbamazepine/oxcarbazepine/ phenytoin.	Severe ID despite good seizure control.	
Benign familial neonatal −infantile epilepsy (BFNIE) #607745 AD	*SCN2A* 182390	Onset: 2 days to 6 months of life. Semiology: cluster of focal clonic or tonic seizures. Frequency: seizures resolve by 12 months.	Normal clinical exam between seizures. EEG: normal background.	Carbamazepine/oxcarbazepine/ phenytoin/lidocaine	Normal development. Low risk of seizure recurrence.	
SCN2A encephalopathy (Neonatal form) #613721 AD	*SCN2A* 182390	Onset: First days of life. Semiology: cluster of focal seizures with tonic componant.	Encephalopathy. EEG: multifocal spikes or BS pattern.	Carbamazepine/phenytoin.	Severe ID, hypotonia, movement disorder	
CDKL5 encephalopathy #300672 X-linked dominant	*CDKL5* 300203	Onset: median age: 6 weeks. Semiology and frequency: tonic seizures, epileptic spasms, typically “hypermotor−tonic−spasm” sequence	Encephalopathy (hypotonia, poor ocular contact) common. EEG: background initially normal than deteriorates.	No effective treatment.	Moderate to severe ID; poor motor control, feeding and sleep problems.	Mostly in females; males have severe phenotypes.