Published in final edited form as:

Acta Paediatr. 2019 January ; 108(1): 184. doi:10.1111/apa.14608.

Growing identification of genetic etiologies for neonatal-onset epilepsies: lessons from the Neonatal Seizure Registry

Amanda G Sandoval Karamian, MD and Fiona M Baumer, MD

Department of Neurology, Division of Child Neurology, Stanford University School of Medicine, Palo Alto, CA

COMMENTARY

Neonatal seizures affect 1–5 per 1,000 live births. While most neonates have seizures secondary to an acute insult, some have a neonatal epilepsy syndrome, typically caused by a genetic mutation and/or a brain malformation (1,2,3). The evaluation and management of these patients is evolving, complicated by the rarity of these disorders. Shellhas et al (2017) have made a significant contribution to the field by assembling one of the largest prospective cohorts of neonates with seizures, 79 of whom had epilepsy. The cohort was rigorously collected using consecutive enrollment and following ACNS guidelines for EEG-confirmation of seizures to standardize diagnosis (4). Practice variations across centers can make assessment of seizure burden challenging. The authors successfully quantified seizure burden with a novel categorical scale, though the clinical significance of these categories is not explained in the study. Despite the impressive collaboration, certain neonatal epilepsy syndromes (i.e. vitamin-responsive epilepsies) were not captured, highlighting the need for larger studies of longer duration.

The study provides an interesting comparison between children with acute symptomatic seizures and those with neonatal epilepsy. The groups were similar in most ways, though neonates with acute symptomatic seizures had a longer duration of EEG monitoring and more subclinical seizures than those with epilepsy. These differences may have been driven by clinical guidelines that dictate all neonates with HIE undergo 72–96 hours of EEG monitoring. As different standards of monitoring were applied, there may have been underestimation of subclinical seizures in the epilepsy group due to this information bias.

The study provides a careful description of the hospital courses of neonates with epilepsy, including their seizure characteristics, work-up and treatment. Most interestingly, 59% of children with neonatal epilepsy who underwent testing had an identifiable genetic cause, including 83% of those with an epileptic encephalopathy. The detailed genetic testing results in table e-1 further highlight the diagnostic yield of such testing, with variants of uncertain

CORRESPONDING AUTHOR, Amanda G Sandoval Karamian, MD, Department of Neurology, Division of Child Neurology, Stanford University, Lucile Packard Children's Hospital, Palo Alto, CA, USA, amandask@stanford.edu, 626-808-3641.

CONFLICTS OF INTEREST

None

URL LINK

URL to the full review on the EBNEO website XXXX

significance in only 5/35 tested. However, even in this cohort taken from level IV NICUs, only 73% underwent genetic testing. The authors conclude that genetic testing is warranted to guide management and prognosis. In considering this conclusion, clinicians must weigh the limitations of this study, which include issues inherent to the observational study design. The clinical rationale behind genetic testing is not detailed in the paper, and it therefore cannot be determined if the untested and tested groups were comparable. Finally, this study does not address whether genetic information influences clinical decision making; for many genetic mutations, there is still little clinical consensus on management.

Despite these caveats, this work illustrates that genetic testing identifies the etiology of neonatal epilepsy in a substantial subset of the population. Diagnostic yield will increase as epilepsy gene panels and whole exome sequencing techniques evolve. Understanding the genetic basis for neonatal epilepsy may change the course of these illnesses, as there is growing evidence that specific genetic conditions benefit from specific medications (i.e. carbamazepine for *KCNQ2* mutations) (5,6). Improved early seizure control may in turn lead to improved cognitive outcomes (3,7).

Acknowledgments

FUNDING

This work was conducted with support from a KL2 Mentored Career Development Award of the Stanford Clinical and Translational Science Award to Spectrum (NIH KL2 TR 001083) and (UL1 TR 001085) (FB).

REFERENCES

1. Vasudevan C, Levene M. Epidemiology and aetiology of neonatal seizures. *Semin Fetal Neonatal Med* 2013; 18(4):185–91. [PubMed: 23746578]
2. Ramantani G Neonatal epilepsy and underlying aetiology: to what extent do seizures and EEG abnormalities influence outcome? *Epileptic Disord* 2013; 15(4):365–75. [PubMed: 24342861]
3. Glass HC. Neonatal seizures: advances in mechanisms and management. *Clin Perinatol* 2014; 41(1): 177–90. [PubMed: 24524454]
4. Shellhaas RA, Chang T, Tsuchida T, Scher MS, Riviello JJ, Abend NS, et al. The American Clinical Neurophysiology Society's guideline on continuous electroencephalography monitoring in neonates. *J Clin Neurophysiol* 2011; 28:611–617. [PubMed: 22146359]
5. Hani AJ, Mikati HM, Mikati MA. Genetics of pediatric epilepsy. *Pediatr Clin North Am* 2015; 62(3):703–22. [PubMed: 26022171]
6. Sands TT, Balestri M, Bellini G, Mulkey SB, Danhaive O, Bakken EH, et al. Rapid and safe response to low-dose carbamazepine in neonatal epilepsy. *Epilepsia* 2016; 57(12):2019–2030. [PubMed: 27888506]
7. Kang SK, Kadam SD. Neonatal Seizures: Impact on Neurodevelopmental Outcomes. *Front Pediatr* 2015; 3:101. [PubMed: 26636052]
8. Shellhaas RA, Wusthoff CJ, Tsuchida TN, Glass HC, Chu CJ, Massey SL, Soul JS, Wiwattanadittakun N, Abend NS, Cilio MR; Neonatal Seizure Registry. Profile of neonatal epilepsies: Characteristics of a prospective US cohort. *Neurology* 2017 8 29;89(9):893–899. . [PubMed: 28733343]