



A Muddy Crystal Ball for Infantile-Onset Epilepsy Outcomes

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A Tale of Two Cohorts: Differing Outcomes in Infantile-Onset Focal Epilepsy

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Objective: Infants with focal-onset epilepsy are an understudied population, requiring additional evaluation for clinical assessment and prognostication. Our goal was to characterize the etiology and natural history of infantile-onset focal epilepsy. **Methods:** We retrospectively identified all infants (0–24 months) with onset of focal epilepsy while resident in Olmsted County, Minnesota, between 1980 and 2018, using the Rochester Epidemiology Project Database. We assessed the impact of etiology on both seizure and neurodevelopmental outcome, and mortality. **Results:** Of 686 children with epilepsy onset <18 years, 125 (18.2%) presented with focal-onset seizures in infancy. Median follow-up for this group was 10.9 years (interquartile range [IQR] 6.2, 19.3). Etiology was identified in 65.6% (structural $N = 62$, genetic $N = 13$, both structural and genetic $N = 3$, metabolic $N = 4$). Of 107 patients followed >2 years, 38 (35.5%) developed drug-resistant epilepsy (DRE). DRE was more likely with younger age at onset, known etiology, and presence of epileptic spasms. Sixty-eight (63.0% of those with follow-up) were developmentally delayed at last follow-up, and known etiology, DRE, and presence of epileptic spasms were significantly associated with delay ($p < .001$ for all). Fifteen patients (12.0%) died at a median age of 7.1 years (IQR 1.7, 21.7), but only one death was seizure related (suspected sudden unexpected death in epilepsy [SUDEP]). Of 20 infants with normal development at onset and no known etiology with >2 years follow-up, none developed DRE, all were seizure-free at last follow-up (95% off antiseizure medications [ASMs]), and all remained developmentally normal. **Significance:** Infantile-onset focal epilepsy accounts for 18% of all epilepsy in childhood, is frequently due to known etiologies, and has a high rate of DRE. However, developmentally normal infants without a known cause appear to have a very favorable course.

Commentary

When you see a little baby with epilepsy, have you ever wondered how she would do when she grows up? Is she going to be free of seizures? Is she going to be able to play and learn just like her friends? And . . . do you, as a doctor, know the answers?

The incidence of epilepsy is highest in infants compared to all age groups, estimated at 70 per 100 000.¹ Focal epilepsy (including epileptic spasms due to a focal lesion) constitutes the largest subgroup.^{2,3} Seizures and developmental outcomes are generally believed to be poor in this population. But is that always true?

The work highlighted in this commentary found that 75% of 167 children with infantile-onset (<24 months of age) epilepsy had focal epilepsy. Let's enjoy the good news first.⁴ After at least 2 years of follow-up, 57% of patients were seizure-free for

at least a year, and almost one-third were able to stop taking anti-seizure medication. Normal cognition at diagnosis, normal neurological examination, normal MRI, absence of EEG background slowing, and an unknown etiology predict seizure freedom.

The not-so-good news is that for those who weren't seizure-free, 35.5% met the criteria for the "D word . . . drug-resistant epilepsy (DRE)." This incidence is higher compared to 22% to 23% in all pediatric age ranges.^{5,6} The factors casting this wicked outcome include cognitive impairment at onset, abnormal neurological examination, EEG background slowing, epileptic spasms, and status epilepticus. Although younger age at

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onset and a known etiology were probably at play, they did not reach statistical significance. This information could enable us to provide better anticipatory monitoring and prompt treatment of those at risk for unfavorable outcomes.

Take epileptic spasm as an example. The authors reported that of the 115 children with focal seizures without spasms at presentation, 15 (13%) eventually developed spasms within about 5 months of median duration. The younger age at onset, cortical dysplasia, and abnormal neurological examination predicts a greater chance of developing epileptic spasms. With this knowledge, we can be more prepared for early detection and provide earlier treatment of infantile spasms, knowing that a shorter lead time to treatment can improve the outcomes in these children.^{7,8}

Whether someone had a good or bad outcome, the answer usually showed by 3 years post-diagnosis. The authors reported that by 3 years post-diagnosis, 90% of the patients had become seizure-free or had DRE. As time passed, more patients achieved seizure freedom, but the proportion of DRE remained stable at 20 years post-diagnosis (37.5%). However, this matter is not as simple as we hope. Initial seizure remission before becoming intractable was reported in 65% to 75% of children with epilepsy. Especially in children with focal epilepsy, intractability may be delayed for many years post-diagnosis and may be preceded by a period of relatively low seizure occurrence or even complete remission.⁶

Shifting gear to etiology, the authors reported a lower-than-expected associated genetic finding, which is likely due to less testing in the past. However, a recent prospective study showed a diagnostic genetic result in 24% of cases using next-generation sequencing technology. Additional yield may be obtained by whole exome sequencing techniques.⁹

This study showed that one-third of patients with normal or mildly delayed development at the diagnosis had worse cognition at the last follow-up. This suggests possible side effects from anti-seizure medications or uncontrolled seizures, and also likely reflects the natural course of some genetic conditions. Let's consider a relatively recent concept of developmental and epileptic encephalopathy (DEE). Developmental and epileptic encephalopathy refers to the coexistence of developmental encephalopathy (directly due to the underlying cause of epilepsy) and epileptic encephalopathy (implying that the epileptic activity causes cognitive impairments).¹⁰ Patients with DEE commonly have infantile-onset epilepsy, often resulting from genetic disorders or structural causes. While not explicitly defined in this study, I believe a large proportion of this cohort meets the definition of DEE. While this study showed that half of the cases had a brain structural abnormality, it is plausible that there's an overlap of patients with underlying genetic conditions who also have structural brain abnormality.

The critical matter is that the progress in molecular biology has provided insights into the pathophysiology of these genetic disorders, allowing the development of precision medicine targeting specific pathological mechanisms. This evolution of treatment approach enables us to think beyond what we currently do in standard practice. While genetic testing is cost-

prohibitive at times, it has become more accessible. With early detection of underlying genetic etiology, a better understanding of outcome predictive factors, and a promising future of precision treatments, excellent outcomes are not impossible.


Lastly, while it is beyond the direct scope of this article, the following findings are difficult to ignore. The incidence of the combined pre and postnatal complications was reported in half of this cohort, along with prematurity (20%) and neonatal seizures (22%). Based on this information, it is conceivable that brain injury (whether detected by imaging or not) might have been more than the 27% reported in this study. What more can be done to prevent these undesirable perinatal complications?

In summary, focal epilepsies are a diverse and poorly understood group of epilepsies. This study gives us a clear view of the outcome spectrum of infantile-onset epilepsies, ranging from excellent seizure control with normal cognition to DRE with severe cognitive impairments and sudden unexpected death in epilepsy. Additionally, the study provides knowledge on outcome predictive factors. Early detection of the unfavorable factors using a physical examination, EEG, MRI, and genetic testing could provide strategic approaches to treatment and monitoring to enable the best possible outcomes we can provide for our patients. Our crystal ball is quite muddy, but I suppose it's getting polished up a bit by this study.

Author's Note

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