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Earlier Is Not Always Better: Outcomes When Epilepsy Occurs in Early Life Versus Adolescence

Immediate Outcomes in Early Life Epilepsy: A Contemporary Account

Berg AT, Wusthoff C, Shellhaas RA, et al. *Epilepsy Behav*. 2019;97:44-50. doi:10.1016/j.yebeh.2019.05.011. Epub 2019 Jun 7. PMID: 31181428

Rationale: Early-life epilepsies include some of the most challenging forms of epilepsy to manage. Given recent diagnostic and therapeutic advances, a contemporary assessment of the immediate short-term outcomes can provide a valuable framework for identifying priorities and benchmarks for evaluating quality improvement efforts. Methods: Children with newly diagnosed epilepsy and onset <3 years were prospectively recruited through 17 US hospitals, from 2012 to 2015 and followed for 1 year after diagnosis. Short-term outcome included mortality, drug resistance, evolution of nonsyndromic epilepsy to infantile spasms (IS) and from IS to other epilepsies, and developmental decline. Multivariable analyses assessed the risk of each outcome. Results: Seven hundred seventy-five children were recruited, including 408 (53%) boys. Median age at onset was 7.5 months (interquartile range [IQR]: 4.2-16.5), and 509 (66%) had onset in the first year of life. Of 22 deaths that occurred within 1 year of epilepsy diagnosis, 21 were children with epilepsy onset in infancy (<12 months). Of 680 children followed ≥6 months, 239 (35%) developed drug-resistant seizures; 34/227 (15%) infants with nonsyndromic epilepsy developed IS, and 48/210 (23%) initially presenting with IS developed additional seizure types. One hundred (23%) of 435 with initially typical development or only mild/equivocal delays at seizure onset, had clear developmental impairment within 1 year after initial diagnosis. Each outcome had a different set of predictors; however, younger age and impaired development at seizure onset were broadly indicative of poorer outcomes. Type of epilepsy and early identification of underlying cause were not reliable predictors of these outcomes. Conclusion: Early-life epilepsies carry a high risk of poor outcome which is evident shortly after epilepsy diagnosis. Onset in infancy and developmental delay is associated with an especially high risk, regardless of epilepsy type. The likelihood of poor outcomes is worrisome regardless of specific clinical profiles.

Pharmacological Outcomes in Teenagers With Newly Diagnosed Epilepsy: A 30-Year Cohort Study

Alsfouk BA, Alsfouk AA, Chen Z, Kwan P, Brodie MJ. *Epilepsia.* 2019;60(6):1083-1090. doi:10.1111/epi.15664. Epub 2019 May 21. PMID: 31111485

Objective: To evaluate the long-term pharmacological outcomes in teenagers with different epilepsies. Method: This study included teenagers aged 13 to 19 years at treatment initiation who were newly treated with antiepileptic drugs (AEDs) at the epilepsy unit of the Western Infirmary in Glasgow, Scotland, between 1 September 1982 and 30 September 2012. Patients were prospectively followed until April 30, 2016, or death, with at least a 2-year follow-up. Results: A total of 332 adolescent patients (53% female; median age 16 years; 54% with generalized epilepsy) were included. At the end of the study, 221 (67%) patients were seizure-free. A higher seizure-free rate was observed in those with generalized compared to focal epilepsy (72% vs 60%, $P = .01$). During the study, 108 patients had relapses after periods of being seizure-free, most commonly due to poor adherence to AEDs (49%, n = 53/108). Antiepileptic drug withdrawal was associated with a high risk of seizure recurrence (70%, n = 26/37), but 56% (n = 61/108) of relapsed patients became seizure-free again by the end of the study, with only 9% (n = 31/332) meeting the International League Against Epilepsy definition of pharmacoresistance during follow-up. Of the 221 seizure-free patients, 83% achieved this on monotherapy. There was no significant difference in efficacy rate between new and standard AED monotherapy (74% vs 77%, $P = .66$). The overall poor tolerability rate of AEDs was 21% (n = 69/332). Among the different new and standard AEDs used as initial monotherapy, lamotrigine was associated with the lowest rate of adverse effects (12%, n = 15/124), while topiramate was associated with the highest rate (56%, n = 5/9). Significance: Teenagers with epilepsy showed good seizure control, particularly those with generalized epilepsy. However, relapse was common and there was high risk of seizure recurrence after treatment withdrawal. Most patients were controlled on monotherapy. As the efficacy of AEDs was comparable, tolerability can be a primary consideration for AED selection in this population.

Commentary

As Child Neurologists, we often remind trainees that children, even adolescents, are not simply "small adults." Pediatric patients have their own diseases, comorbidities, and outcomes. However, it is also important to remind ourselves that not all pediatric patients are the same, either. Infants and toddlers are not simply "smaller children." Developmental outcomes, pharmacoresistance, and mortality vary greatly between children with epilepsy onset during adolescence compared to onset early in life. Two recently published articles remind us of this point.

Epilepsy, both focal and generalized, can occur at any time during childhood. Alsfouk et al recently examined the outcomes of teenagers with newly diagnosed epilepsy and came to the overall conclusion that these patients were likely to have good seizure control, good responsiveness to medication, low risk of sudden unexpected death in epilepsy or other seizure-related mortality, but were also at high risk for seizure relapse after treatment withdrawal. However, when Berg and colleagues reviewed outcomes of early life (onset < age 3 years) epilepsy, the results were remarkably different. Pharmacoresistance was common, mortality was higher, and it was concluded that early onset epilepsy, especially onset within the first year of life, is a high-risk situation until proven otherwise.

How can 2 studies on pediatric epilepsy outcomes arrive at such vastly different conclusions? Can age alone really be that much of a determining factor? If the same children had the same epilepsy, but onset occurred later, would the outcome be better? The answer is a simple "yes" . . . and "no." In reality, the issue is far more complicated than just the immaturity of the pediatric brain. The differences are most likely due to a combination of factors, including electroclinical syndrome, etiology, as well as the effects of continuing seizures and medication on developing networks.

Electroclinical syndrome classification can be helpful in guiding physicians toward preferred treatments and recommended evaluations, as well as counseling families on expected outcomes and comorbidities. Syndromes with onset in adolescence include the generalized genetic epilepsy syndromes (juvenile myoclonic epilepsy, juvenile absence epilepsy, and epilepsy with generalized tonic-clonic seizures alone). These syndromes are well-characterized, with approximately 2/3 of patients enjoying seizure freedom, but less than 20% being able to remain seizure-free when medications were discontinued.[1] Indeed, 53% of Alsfouk's cohort was classified as one of these 3 syndromes, with 72% of the patients with generalized epilepsy enjoying long-term seizure freedom. However, only 30% of all patients, focal or generalized, were able to remain seizure-free after withdrawing medications. By comparison, electroclinical syndromes that present in the first year of life include epileptic encephalopathies such as West syndrome, Ohtahara syndrome, Dravet syndrome, epilepsy of infancy with migrating focal seizures, myoclonic encephalopathy in nonprogressive disorders, and myoclonic epilepsy in infancy.[2] Like the generalized genetic epilepsy syndromes, these syndromes are also well-characterized, with the majority demonstrating high risk of medical intractability.[3] As expected, 35% of the infants in Berg's study met criteria for pharmacoresistance within the year after epilepsy diagnosis, compared to 9% Alsfouk's teenagers.

Etiology is also an important determining factor in epilepsy outcome. Abnormal neuroimaging is an independent risk factor for intractable epilepsy that occurs early and is enduring, as well as decreased remission.[3-5] In Alsfouk's study of adolescents, epilepsy etiology was classified as structural in 12%. By comparison, structural etiology has been identified in up to 35% to 40% of children with early onset epilepsy.[2,3,6] Genetic variants are also an important etiological factor to consider. While genetic variants can cause epilepsy of variable clinical severity, they are also associated with early onset epilepsy and epileptic encephalopathies, such as Dravet and West syndromes.[2,6,7] Genetic testing in children with epilepsy onset prior to age 3 years has revealed pathogenic variants in up to 40%.[6]

Finally, we must consider how continuing seizures and chronic medication use affect growing and developing brains. When children with epilepsy onset prior to age 3 years underwent formal neuropsychometric testing, age at epilepsy onset was found to be the single most reliable predictor of developmental outcome, with earlier age of onset being associated with lower developmental quotient.[8] There was no correlation between developmental outcome and underlying pathology, suggesting the developmental decline was related to the epilepsy and seizures, rather than the underlying cause.[8] Continued seizures as a cause of development decline is supported by the observation by Berg that lower full scale IQ (FSIQ < 80) was correlated with younger age of epilepsy onset only in the children with ongoing seizures due to pharmacoresistance.[9] In addition, children who undergo surgical resection for epilepsy demonstrate improvements in neuropsychological functioning, even though one would expect some degree cognitive decline following a resection.[10] Furthermore, while continued seizures can have a detrimental effect, and the use of antiseizure medications (ASMs) are an essential part of treating seizures, these medications are not benign. Boshuisen has demonstrated that withdrawing ASMs after epilepsy surgery was associated with increased IQ, even when controlled for confounders, such as age at epilepsy surgery and preoperative IQ score.[11]

In summary, there are significant differences in epilepsy outcomes and comorbidities, depending on age of onset due to multiple factors. Does this mean we take a defeatist's approach to early onset epilepsies and accept the likelihood of pharmacoresistance and developmental disabilities? No! Does this mean we view adolescent onset epilepsy as "easy" and "uncomplicated?" Certainly not! It is important to recognize these populations as different, understand the epilepsy syndromes that occur in these age groups, so that we can apply this information to use the best treatments possible, screen for

known comorbidities, and provide appropriate counseling to patients and families.

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