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Original Article

Initial Treatment for Nonsyndromic Early-Life Epilepsy: An Unexpected Consensus

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ABSTRACT

OBJECTIVE: There are no evidence-based guidelines on the preferred approach to treating early-life epilepsy. We examined initial therapy selection in a contemporary US cohort of children with newly diagnosed, nonsyndromic, early-life epilepsy (onset before age three years). **METHODS:** Seventeen pediatric epilepsy centers participated in a prospective cohort study of children with newly diagnosed epilepsy with onset under 36 months of age. Details regarding demographics, seizure types, and initial medication selections were obtained from medical records. **RESULTS:** About half of the 495 enrolled children with new-onset, nonsyndromic epilepsy were less than 12 months old at the time of diagnosis (n = 263, 53%) and about half (n = 260, 52%) had epilepsy with focal features. Of 464 who were treated with monotherapy, 95% received one of five drugs: levetiracetam (n = 291, 63%), oxcarbazepine (n = 67, 14%), phenobarbital (n = 57, 12%), topiramate (n = 16, 3.4%), and zonisamide (n = 13, 2.8%). Phenobarbital was prescribed first for 50 of 163 (31%) infants less than six months old versus seven of 300 (2.3%) of children six months

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or older ($P < 0.0001$). Although the first treatment varied across study centers ($P < 0.0001$), levetiracetam was the most commonly prescribed medication regardless of epilepsy presentation (focal, generalized, mixed/uncertain). Between the first and second treatment choices, 367 (74%) of children received levetiracetam within the first year after diagnosis. **CONCLUSIONS:** Without any specific effort, the pediatric epilepsy community has developed an unexpectedly consistent approach to initial treatment selection for early-life epilepsy. This suggests that a standard practice is emerging and could be utilized as a widely acceptable basis of comparison in future drug studies.

Keywords: epilepsy, antiepileptic drugs, generalized seizures, focal seizures, levetiracetam, oxcarbazepine, phenobarbital

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Introduction

Over the last twenty years, many new antiseizure medications have become available. Medications typically receive US Food and Drug Administration approval for use based upon add-on trials in adults with pharmacoresistant focal epilepsy. Once approved, however, medications may also be prescribed for patients of all ages.[1] With the exception of infantile spasms,[2,3] there are no evidence-based treatment guidelines or published opinion-based recommendations regarding the preferred approach for prescribing antiseizure medications for the optimal treatment of early-life epilepsy. A working group of the International League Against Epilepsy (ILAE) was tasked with the development of such guidelines but was unable to do so because of the lack of high-quality published evidence.[4]

Nonsyndromic early-life epilepsies, forms of epilepsy that do not fit clinical criteria for West syndrome or other well-recognized electroclinical syndromes, affect about 8000 children under three years of age each year in the United States.[5,6] Although there are legitimate concerns about the effect of antiseizure medications on the developmental trajectory of the young child's brain,[7-9] failure to control early-life seizures may be associated with adverse neurodevelopmental outcomes.[10] More than 20 antiseizure medications are now available, but there are few data to suggest that one antiseizure medication is more effective than another.

In light of the seriousness of the outcomes in early-life epilepsies, the absence of evidence-based guidelines or even opinion-based recommendations on the preferred approach to treating these epilepsies represents an important gap in providing optimal care. We examined the selection of initial medications in children with nonsyndromic early-life epilepsy in an effort to identify opportunities for rational standardization of practice.

Methods

From January 2013 to March 2015, 17 US pediatric epilepsy centers participated in a prospective observational cohort study of infants and toddlers with newly diagnosed epilepsy with onset under 3 years of age. The centers were all members of the Pediatric Epilepsy Research Consortium, a nonprofit organization of pediatric epilepsy centers whose mission is to facilitate collaborative clinical research designed to answer practical questions related to the care of children with epilepsy. The institutional review board at each participating hospital approved this study, and a parent or a guardian of every enrolled child provided written informed consent.

Children were eligible if they were less than 36 months old at the onset of epilepsy and no older than 42 months when newly diagnosed with epilepsy at one of the participating centers. Children were considered to have new-onset epilepsy if they had unprovoked seizures on two or more separate days. To reflect recent recommendations[11] we also included children who presented with a single seizure or multiple seizures on a single day if, based on the underlying cause or electrographic features, the children were judged by the treating physician to be at very high risk of recurrence and epilepsy treatment was initiated. Only children who could not be diagnosed at their initial evaluation with a specific epilepsy syndrome that might influence treatment selection were included in this analysis. Genetic test results that became available after treatment initiation for children whose initial presentation did not fit a specific epilepsy syndrome did not lead to exclusion because clinicians had made their initial treatment decisions without those results. Infants with West syndrome or infantile spasms and other specific electroclinical syndromes (e.g., Dravet, Ohtahara and Lennox-Gastaut syndromes, myoclonic-atonic epilepsy, early-onset absence epilepsy, and benign familial infantile epilepsy) were excluded. Recommendations already exist for West syndrome/infantile spasms; the most appropriate treatments are adrenocorticotropic hormone (ACTH), prednisolone, or vigabatrin.[2,3] For the other excluded syndromes, especially Dravet syndrome, there are opinion pieces[12,13] and some evidence from either observational or randomized trials to support certain treatment preferences.[14]

Data were abstracted from standardized medical chart reviews. Trained research assistants extracted the information, which was reviewed by the site principal investigator (PI) (a pediatric epileptologist) who oversaw the coding of data according to a structured code manual and manual of operations provided by the study. All data were then entered into a central REDCap[15] database housed at Northwestern University. All data were centrally reviewed by the lead study coordinators, with final review of each case by the principal investigator (ATB). Questions were returned to the sites until all questions had been satisfactorily addressed. Demographic data (sex, race, ethnicity, insurance type) were directly extracted from the electronic medical record. Distance from site was based on home address provided in the record and, when necessary, an internet search to determine the distance from home to the hospital. A history of prior provoked seizures (febrile, acute neonatal, etc.) was taken from the history recorded in the clinician's electronic medical record notes. For this study, age at onset was based on date of birth without correction for gestational age. The descriptors "focal" and "generalized" for type of epilepsy and seizure onset were taken as used in the medical records. When interpretation was needed, "focal" was used for findings that were completely lateralized or markedly asymmetric. "Generalized" was used for findings that were bilaterally symmetric. When information indicated both clear focal and generalized features or was insufficient to interpret, the term "mixed/uncertain" was applied.

Selection of epilepsy treatments was according to the clinicians' best judgment and was not dictated by study participation. Specific rationale for individual clinical decision making or medication selection was not systematically queried. Although consensus-based dosing strategies were suggested to the participating centers, there was no effort to enforce any specific medication selection, dosing, or escalation plan. For children not on medication at the time of their diagnostic electroencephalography, the first medication was considered to be the one started immediately after diagnosis. Some children were already on an antiseizure medication at the time of epilepsy diagnosis. If that medication was continued as his or her epilepsy therapy, it was considered the first medication, but if it was discontinued and a new medication started, the new medication was considered to be the first

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