Behavior Problems in Childhood Absence Epilepsy: A Chicken or Egg Problem

Pretreatment Behavior and Subsequent Medication Effects in Childhood Absence Epilepsy.

Shinnar RC, Shinnar S, Cnaan A, Clark P, Dlugos D, Hirtz DG, Hu F, Liu C, Masur D, Weiss EF, Glauser TA; Childhood Absence Epilepsy Study Group. *Neurology* 2017;89(16):1698–1706. doi: 10.1212/WNL.0000000000004514.

OBJECTIVE: To characterize pretreatment behavioral problems and differential effects of initial therapy in children with childhood absence epilepsy (CAE). METHODS: The Child Behavior Checklist (CBCL) was administered at baseline, week 16-20, and month 12 visits of a randomized double-blind trial of ethosuximide, lamotrigine, and valproate. Total problems score was the primary outcome measure. RESULTS: A total of 382 participants at baseline, 310 participants at the week 16-20 visit, and 168 participants at the month 12 visit had CBCL data. At baseline, 8% (95% confidence interval [CI] 6%-11%) of children with CAE had elevated total problems scores (mean 52.9 ± 10.91). At week 16-20, participants taking valproic acid had significantly higher total problems (51.7 [98.3% CI 48.6-54.7]), externalizing problems (51.4 [98.3% CI 48.5-54.3]), attention problems (57.8 [98.3% CI 55.6-60.0]), and attention-deficit/hyperactivity problems (55.8 [98.3% CI 54.1-57.6]) scores compared to participants taking ethosuximide (46.5 [98.3% CI 43.4-49.6]; 45.8 [98.3% CI 42.9-48.7]; 54.6 [98.3% CI 52.4-56.9]; 53.0 [98.3% CI 51.3-54.8]). Lack of seizure freedom and elevated week 16-20 Conner Continuous Performance Test confidence index were associated with worse total problems scores. At month 12, participants taking valproic acid had significantly higher attention problems scores (57.9 [98.3% CI 55.6-60.3]) compared to participants taking ethosuximide (54.5 [95% CI 52.1-56.9]). CONCLUSIONS: Pretreatment and ongoing behavioral problems exist in CAE. Valproic acid is associated with worse behavioral outcomes than ethosuximide or lamotrigine, further reinforcing ethosuximide as the preferred initial therapy for CAE.

Commentary

Which came first, the chicken or the egg? There is no answer to this age-old question, and although rhetorical, it is relevant for any study evaluating behavior problems associated with epilepsy. A reigning controversy among epilepsy scholars is whether seizures beget behavior problems or vice versa. Work with new-onset seizure populations has effectively suggested that behavior problems are present early in the disease course and may reflect overlapping pathophysiology. However, the gold standard for evidence is still in treatment outcomes. Do we first treat behavior or do we first treat seizures, or more importantly, can anticonvulsant treatment simultaneously improve both behavior problems and epilepsy?

Shinnar and colleagues boldly attempt to confront this dichotomy, assessing treatment effects based on serial behavior rating scales. The sample comes from the Childhood Absence Epilepsy (CAE) Study, a large-scale clinical trial that compared lamotrigine, ethosuximide, and valproic acid (1). Baseline behavior ratings were primarily done with the Child Behavior Checklist (CBCL), though measures of attention (continuous performance) and executive function (Wisconsin Card Sort) were also done. The original study found that ethosuximide and valproic acid were superior to lamotrigine for seizure control. However, the conclusion from this analysis is that ethosuximide offers better behavioral outcomes.

Right away, this conclusion seems suspect. After all, valproic acid and lamotrigine have a sizable evidence base affirming their utility for psychiatric conditions (2). Both are mainstays of treatment not only for bipolar disorder but also, in the case of valproate, for impulsivity in pediatric patients (3, 4). Ethosuximide has little if any evidence suggesting such efficacy (5, 6). So this report is novel, purely in being a large clinical trial suggesting that ethosuximide yields notable behavioral improvement.

However, a closer look reveals the challenge that often hampers clinical trials in epilepsy. Often a behavioral baseline is not obtained or appropriate measures are not used. Fortunately, neither of those problems are serious flaws in this study. Although some may question whether parent reports or continuous performance tests may be considered valid, even structured diagnostic interviewing from clinician raters may not provide superior identification of psychiatric comorbidity in pediatric patients (7, 8).

Epilepsy Currents, Vol. 18, No. 2 (March/April) 2018 pp. 97–98

Instead, the difficulty may lie in how the measures are used. CBCL scores are divided into two main classifications: broad band, which includes general categories, such as internalizing, externalizing, and total problems, and narrow band, which includes specific categories, such as attention, anxiety, or depression. Raw scores are converted to *t*-scores that allow comparisons with normative data. A *t*-score of 50 reflects the 50th percentile, the normative mean. A *t*-score of 60 reflects one standard deviation above the mean, and a *t*-score of 70 reflects two standard deviations above the mean. Many studies using the CBCL separate narrow band and broad band scoring by using different *t*-score thresholds of 60 (broad band) or 65 (narrow band) to reflect borderline clinical significance; this is still well above the normative mean but below the threshold of 70 used in this study. In this study, using a *t*-score threshold of 70 may have excluded participants who were still markedly impaired. Yet even at that level, 15% of the sample had clinically significant scores for attention problems, reinforcing that in CAE, attention issues are notably overrepresented.

However, the outcomes analysis was based on average *t*-scores in the entire sample, not on thresholds. Most participants scored well below thresholds of even borderline clinical significance. Clinically, there is very little meaningful difference between *t*-scores near the normative mean, for example, 50 to 54 or 55 to 59, yet this degree of difference (54.5 versus 57.9) is the main basis for determining superiority of treatments. Of note, neither broad band nor narrow band scores convincingly correlate with psychiatric diagnoses, notwithstanding algorithmic attempts in recent test versions. Broad band categories, including the total problems score, reflect heterogeneous questionnaire items and are very difficult to interpret as stand-alone values.

Correctly, Shinnar and colleagues provide us with full data so we may make additional queries. Rather than an average, it may be more meaningful to assess the absolute number of participants who report *t*-scores for attention problems above the threshold of 70. We then see that the valproate group (24/131) had more severe problems at baseline than the ethosuximide group (13/131), though their problems were roughly similar to those of the lamotrigine group (21/120). At the end of the study there was some association between worse behavior and worse seizure control, yet overall improvements were still noted in each treatment group. By absolute numbers, and ignoring dropouts, 15 patients (24 versus 9) in the valproate group no longer had *t*-scores for attention above 70. By comparison, 12 patients (13 versus 1) in the ethosuximide group fell below threshold, and 20 patients (21 versus 1) in the lamotrigine group appeared to similarly improve. Although intriguing, these findings are compromised by the differential dropout rate, which was markedly worse for the lamotrigine group (73%) than for ethosuximide (49%) or valproate (48%) groups.

Counter to the authors' conclusions, it may be that participants with worse attention simply dropped out. Or it could be that lamotrigine actually performed the best; more patients in this group fell below threshold than those receiving other treatments. Even if the authors are correct in their conclusions, it still cannot be discounted that the ethosuximide group was healthier, in terms of threshold attention problems, at baseline.

Such limitations cannot be ignored. The idea that anticonvulsants vary in terms of effects on behavior and attention is reasonable, but without addressing the rating nuances and accounting for dropouts, we can only conclude that all three treatments are effective. Yet this report is still groundbreaking, perhaps for an unexpected reason. Rather than proving superiority of a single treatment, Shinnar and colleagues show that ethosuximide, an anticonvulsant without a track record of treating behavior, effectively improves both seizures and behavior in CAE.

The implications of this finding are striking. CAE is well known to include attention problems well beyond the level expected based on seizure frequency and severity (9). It is now even more plausible to consider that attention problems result from the underlying pathophysiology of CAE. The behavior improvements observed cannot be explained solely by improved seizure control or superior side-effect ratings as these parameters were comparable among treatments. Ultimately, the behavior problems may not result from the epilepsy or vice versa. Like the age-old chicken and egg conundrum, the etiologic problem with behavior issues and epilepsy may lie with the query itself. The chicken and egg are one and the same. The fact that even a medicine such as ethosuximide improves both seizures and behavior shows that at least attention problems and CAE may also be one and the same, independent of absence seizure episodes yet not independent of CAE pathophysiology.

by Jay Salpekar, MD

References

1. Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, Clark PO, Capparelli EV, Adamson PC, Childhood Absence Epilepsy Study Group. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. *N Engl J Med* 2010;362:790–799.
2. Mula M. Investigating psychotropic properties of antiepileptic drugs. *Expert Rev Neurother* 2013;13:639–646.
3. Donovan SJ, Nunes EV, Stewart JW, Ross D, Quitkin FM, Jensen PS, Klein DF. "Outer-directed irritability": a distinct mood syndrome in explosive youth with a disruptive behavior disorder? *J Clin Psychiatry* 2003;64:698–701.
4. Hollander E, Soorya L, Wasserman S, Esposito K, Chaplin W, Anagnostou E. Divalproex sodium vs. placebo in the treatment of repetitive behaviours in autism spectrum disorder. *Int J Neuropsychopharmacol* 2006;9:209–213.
5. Verrotti A, Moavero R, Panzarino G, Di Paolantonio C, Rizzo R, Curatolo P. The challenge of pharmacotherapy in children and adolescents with epilepsy-ADHD comorbidity. *Clin Drug Investig* 2018;38:1–8.
6. Aldenkamp A, Besag F, Gobbi G, Caplan R, Dunn DW, Sillanpaa M. Psychiatric and Behavioural Disorders in Children with Epilepsy (ILAE Task Force Report): Adverse cognitive and behavioural effects of antiepileptic drugs in children. *Epileptic Disord* 2016 May 16. ePub ahead of print.
7. Hesdorffer DC, Baldin E, Caplan R, Berg AT. How do we measure psychiatric diagnoses? Implications of the choice of instruments in epilepsy. *Epilepsy Behav* 2014;31:351–355
8. Ott D, Siddarth P, Gurbani S, Koh S, Tournay A, Shields WD, Caplan R. Behavioral disorders in pediatric epilepsy: unmet psychiatric need. *Epilepsia* 2003;44:591–597.
9. Killory BD, Bai X, Negishi M, Vega C, Spann MN, Vestal M, Guo J, Berman R, Danielson N, Trejo J, Shisler D, Novotny EJ Jr, Constable RT, Blumenfeld H. Impaired attention and network connectivity in childhood absence epilepsy. *Neuroimage* 2011;56:2209–2217.