Childhood Absence Epilepsy: What Is All the Distraction About?

Pretreatment EEG in Childhood Absence Epilepsy: Associations With Attention and Treatment Outcome.

Dlugos D, Shinnar S, Cnaan A, Hu F, Moshé S, Mizrahi E, Masur D, Sogawa Y, Le Pichon JB, Levine C, Hirtz D, Clark P, Adamson PC, Glauser T; Childhood Absence Epilepsy Study Team. *Neurology* 2013;81:150–156.

OBJECTIVE: In children with newly diagnosed childhood absence epilepsy (CAE), determine pretreatment EEG features and their associations with baseline neuropsychological function and short-term treatment outcome. **METHODS:** In a multicenter, randomized clinical trial, patients with CAE underwent a pretreatment, 1-hour video-EEG and neuropsychological testing with freedom-from-failure and seizure-freedom (SF) outcome assessed at the 16- to 20-week visit. **RESULTS:** Detailed evaluation of the pretreatment EEG was possible for 99.8% of participants (445/446). Median time to first seizure was 6.0 minutes (range 0–59 minutes), median number of seizures was 5 (range 1–60), and median seizure duration was 10.8 seconds (range 3.3–77.6 seconds). Median duration of shortest seizure per EEG was 7.5 seconds (range 3.0–77.6 seconds). Seizure frequency was not associated with baseline measures of attention, executive function, or treatment outcome. Presence of a seizure lasting ≥ 20 seconds was noted in 29% of subjects (129/440); these children had higher median omissions T score on the Conners Continuous Performance Test (56.3 vs 51.6, $p = 0.01$). Patients with a shortest seizure of longer duration were more likely to demonstrate treatment success by both freedom-from-failure ($p = 0.02$) and SF ($p = 0.005$) criteria, even after controlling for age, treatment group, and number of seizures, with good predictive value (area under the curve 78% for SF). **CONCLUSIONS:** EEG reliably and quickly confirms CAE. Occurrence of a seizure ≥ 20 seconds, but not overall seizure frequency, was associated with differential baseline measures of attention. Patients whose shortest pretreatment EEG seizure was longer in duration were more likely to achieve SF, regardless of treatment.

Commentary

The study by Dlugos et al. adds to the important information on impaired attention, measured with the Continuous Performance task (CPT), in childhood absence epilepsy (CAE) that has emanated from the large multisite treatment study CAE by Glauser and colleagues (1–3). About 36% of CAE have impaired attention with errors of omission rather than of commission before treatment that improve in 26% of those randomized to valproate, 43% of those randomized to ethosuximide, and 47% of the lamotrigine treated patients (3). The attentional impairment, however, worsened in the valproate cohort overall. These findings are evident 16 to 20 weeks (3) and 12 months (1) after beginning treatment.

Dlugos et al.'s EEG study has shown that duration of seizures is differentially associated with the attentional impairment and treatment effect. Those children who experienced seizures lasting 20 seconds or more had significantly more errors of omission 16 to 20 weeks after starting treatment with one of the three previously mentioned antiepileptic drugs

(AEDs). However, in terms of the treatment effect, freedom from failure and seizure freedom were significantly related to longer duration of the shortest seizure and longer median duration of all seizures irrespective of treatment arm.

What do these findings mean in terms of advancing our understanding of the nature of the attentional impairment in CAE? This question is particularly relevant because the baseline CPT in Dlugos et al.'s study was not administered while the children were having an EEG recording. The CPT findings, therefore, reflect some combination of ictal and interictal attentional impairments, as originally proposed by Mirsky et al. (4). But recent fMRI/EEG studies in CAE with and without CPT and fMRI studies during CPT shed some light on what is distracting these children.

An fMRI/EEG study of 22 children with CAE whose AEDs were withheld during the 48 hours prior to the study demonstrated increased activation of the thalamus, frontal, primary visual, auditory, sensory, and motor cortex but deactivation in lateral and medial parietal, cingulate, and basal ganglia during both ictal and interictal spike wave discharges (5). Furthermore, errors of omission on the CPT that occurred during a seizure were associated with increased and decreased activation in these same thalamocortical regions. Most interestingly, not all seizures involved impaired performance on the CPT

and abnormal thalamocortical activity. In fact, normal CPT performance occurred during the seizures with the shortest duration. Similar to Dlugos et al.'s EEG findings, short duration of seizures appears to not be associated with attentional impairment in CAE. Increased connectivity in the thalamus and extensive decrease in connectivity in the default-mode network, dorsal attention network, central executive network, and salience network also occurred during spike wave discharges in the 16 CAE youth studied by Zhang et al. (6).

But not all absence seizures involve impaired attention and prevalent attention deficit hyperactivity disorder (ADHD); the inattentive type in CAE is not associated with seizure frequency and control (7). Furthermore, the findings of the CAE multisite study suggest that despite freedom from failure and decrease in seizure frequency, 49% of the children on valproate, 32% of those on ethosuximide, and 26% on lamotrigine continued to have deficits in attention 16 to 20 weeks and 12 months after beginning treatment (1, 3). Together, these findings emphasize that these children also have interictal poor attention irrespective of seizure control.

Similar high rates of the inattentive type of ADHD (see review in [8]) in children with localization related epilepsy and in pediatric CNS disorders, such as traumatic brain injury (see review in [9]) suggest that the interictal impaired attention of CAE might be a nonspecific symptom of widespread CNS involvement of the attentional network. Identification of the interictal mechanisms of the deficits in attention—as well as the shared and distinct features of the ictal attentional impairment in children with different epilepsy syndromes—is needed to delineate the underlying mechanisms. A multisite fMRI, EEG, and CPT study on a large sample of children with these different epilepsy syndromes is needed to begin to bridge this important gap in our knowledge.

The poor treatment response of the deficits in attention in the multisite CAE study is an additional reminder, as repeatedly shown over the past two decades, that CAE is not a benign disorder. Impaired attention can hinder children's academic performance, communication, and social relationships, areas of functioning that are impaired in children with epilepsy (see review in [8]) and impact the long-term outcome (10) and quality of life of these children (11). The findings of the CAE multisite study clearly highlight the need to screen every child with CAE for an attentional impairment and the unmet and untreated need of these children. They also underscore the need for focused intervention for this comorbidity. Although there appears to be a treatment effect of stimulants in children with epilepsy and ADHD, the possibility of increased seizure frequency needs to be ruled out in both children with good and poor seizure control [8]. Impaired attention in CAE and other pediatric epilepsy syndromes at onset of these disorders (see review in [8]) and prior to treatment further emphasize the theoretical and clinical importance of pursuing both basic science and treatment studies to address this important comorbidity and its treatment.

Finally, the lack of an association between the EEG findings and measures of executive function in Dlugos et al.'s study might appear surprising given the predominant involvement of the frontal lobe in CAE. However, the lag in maturation of executive functions in children is attributed to the late occurring frontal lobe morphometric changes involving volume and thickness during late childhood and adolescence (12). The young age range of the children in Dlugos et al., 2.5 to 13 years, probably underlies this finding.

by Rochelle Caplan, MD

References

1. Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, Clark PO, Adamson PC; Childhood Absence Epilepsy Study Team. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy: Initial monotherapy outcomes at 12 months. *Epilepsia* 2013;54:141–155.
2. Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, Clark PO, Capparelli EV, Adamson PC. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. *N Engl J Med* 2010;362:790–799.
3. Masur D, Shinnar S, Cnaan A, Shinnar RC, Clark P, Wang J, Weiss EF, Hirtz DG, Glauser TA; Childhood Absence Epilepsy Study Group. Pretreatment cognitive deficits and treatment effects on attention in childhood absence epilepsy. *Neurology* 2013;81:1572–1580.
4. Mirsky AF, Van Buren JM. On the nature of the “absence” in centrencephalic epilepsy: A study of some behavioral, electroencephalographic and autonomic factors. *Electroencephalog Clin Neurophysiol* 1965;18:334–348.
5. Berman R, Negishi M, Vestal M, Spann M, Chung MH, Bai X, Purcaro M, Motelow JE, Danielson N, Dix-Cooper L, Enev M, Novotny EJ, Constable RT, Blumenfeld H. Simultaneous EEG, fMRI, and behavior in typical childhood absence seizures. *Epilepsia* 2010;51:2011–2022.
6. Zhang Z, Liao W, Wang Z, Xu Q, Yang F, Mantini D, Jiao Q, Tian L, Liu Y, Lu G. Epileptic discharges specifically affect intrinsic connectivity networks during absence seizures. *J Neural Sci* Oct. 2013. In press.
7. Caplan R, Siddarth P, Stahl L, Lanphier E, Vona P, Gurbani S, Koh S, Sankar R, Shields WD. Childhood absence epilepsy: Behavioral, cognitive, and linguistic comorbidities. *Epilepsia* 2008;49:1838–1846.
8. Hamiwka L, Jones JE, Salpekar J, Caplan R. Child psychiatry: Special edition on the future of clinical epilepsy research *Epilepsy Behav* 2011;22:38–46.
9. Eme R. ADHD: An integration with pediatric traumatic brain injury. *Expert Rev Neurother* 2012;12:475–483.
10. Wirrell E. Natural history of absence epilepsy in children. *Can J Neurol Sci* 2003;30:184–188.
11. Baca C, Vickrey BG, Caplan R, Vassar D, Berg AT. Psychiatric and medical comorbidity and quality of life outcomes in childhood-onset epilepsy. *Pediatrics* 2011;128:1532–1543.
12. Raznahan A, Shaw P, Lalonde F, Stockman M, Wallace GL, Greenstein D, Clasen L, Gogtay N, Giedd JN. How does your cortex grow? *J Neurosci* 2011;31:7174–7177.