Pharmacoresistance and Cognitive Delays in Children: A Bidirectional Relationship

Age at Onset of Epilepsy, Pharmacoresistance, and Cognitive Outcomes: A Prospective Cohort Study.


OBJECTIVES: Increasing evidence suggests that uncontrolled seizures have deleterious effects on cognition and behavior, particularly in the developing brain. METHODS: In a community-based cohort, 198 children, aged < 8 years with new-onset epilepsy were followed prospectively and reassessed with the Wechsler Intelligence Scales for Children, Third Edition (WISC-III) 8–9 years later. Linear regression analyses with interactions between age at onset (age) and pharmacoresistance (PR) were used to test whether earlier onset conveyed greater vulnerability to the effects of uncontrolled seizures. Full-scale IQ (FSIQ) and the 4 subdomain scores were examined. Adjustment for adaptive behavior scores in a subset was performed. A dichotomous indicator for IQ < 80 or > 80 was used to permit inclusion of children who were not tested, particularly those who were untestable. RESULTS: FSIQ was not correlated with age. PR was associated with an 11.4 point lower FSIQ (p = 0.002) and similar decrements in each WISC-III domain. There were substantial age-PR interactions for FSIQ (p = 0.003) and 3 domain scores, indicating a lessening impact of PR with increasing age. The dichotomous IQ indicator was strongly correlated with age at onset in the pharmacoresistant group (p < 0.0001) and not in the non-pharmacoresistant group (p = 0.61). Adjustment for adaptive behavior measured near onset did not alter the conclusions. CONCLUSIONS: Uncontrolled seizures impair cognitive function with effects being most severe in infancy and lessening with increasing age at onset. These findings further emphasize the need for early aggressive treatment and seizure control in infants and young children.

Developmental Outcomes of Childhood-Onset Temporal Lobe Epilepsy: A Community-Based Study.


PURPOSE: To assess the impact of childhood-onset temporal lobe epilepsy (TLE) on the attainment of normative developmental tasks and identify predictors of long-term developmental outcomes. METHODS: In 1992–1993, a prospective longitudinal cohort study of childhood-onset TLE was commenced in the State of Victoria, Australia. At review in 2004–2006, we assessed developmental tasks, which are age-specific individual psychosocial achievements tied to particular phases of the lifespan. The cohort comprised 54 individuals (33 female) with a mean age of 20 years (range 12–29), and mean age at TLE onset of 6 years (range 0.2–15). KEY FINDINGS: Individuals were clustered into three groups representing distinct developmental trajectories: (1) a Normal group (52%) who achieved most of their developmental tasks, (2) an Altered group (37%) who achieved some, and (3) a Delayed group (11%) who achieved few. The groups showed significant cognitive differences, with the Normal group outperforming the Altered and Delayed groups on a range of measures (p < 0.05). Multiple discriminant function analysis indicated that membership of the groups was independently predicted by the chronicity of seizures, cognitive functioning, having surgically remediable epilepsy, and gender (p < 0.001). Seizure chronicity and cognition discriminated between all three trajectories, while surgical intervention and gender primarily discriminated between the Altered and Delayed trajectories. SIGNIFICANCE: Childhood-onset TLE can disrupt achievement of normative developmental tasks that is independently predicted by medical, biologic, and cognitive factors. Assessment of developmental tasks across the lifespan provides a practical framework for guiding prognostic counseling of patients and families.
Commentary

In children with epilepsy, particular attention was always given to examining and predicting cognitive co-morbidities, for obvious reasons. Parents, educators, and healthcare providers need to know: 1) whether an epilepsy diagnosis automatically commits the child to cognitive delays and challenges, and 2) how to identify children at highest risk for such delays for timely targeting of early intervention. These two delicately interrelated, but independently significant, questions are addressed in a growing body of relevant literature, most recently enriched by two valuable population-based studies chosen for this commentary.

At face value, the work highlighted here essentially corroborates well-established facts: First, consistent with earlier studies (1), Berg et al. confirm that as a cohort, children with epilepsy are at a cognitive disadvantage with a mean full scale IQ score of 94.2, falling within the normal range but less than the expected standardized mean of 100. Second, Wilson et al. confirm that as individuals, the majority of children with epilepsy do attain normal development, with 52% of their children with temporal lobe epilepsy achieving most of their developmental milestones by early adulthood—in agreement with earlier literature documenting favorable developmental outcomes in up to two thirds of children with epilepsy (2). Third, both studies highlight the role of seizure burden on development through either dissecting the detrimental cognitive implications of earlier age at seizure onset in children with pharmacoresistant epilepsy in Berg et al., or documenting the correlations between longer chronicity of seizures and higher rates of altered or delayed developmental trajectories in Wilson et al. At a deeper level, these papers lead to many more interesting mechanistic questions.

With a high seizure burden so clearly correlated with poorer cognitive outcomes, the logically inferred conclusion is often a call for earlier identification of pharmacoresistance so more aggressive treatments can be done early. The expectation then is that with seizures removed, cognitive delays will be avoided. Is the logic so straightforward?

There is no question that frequent seizures have a detrimental effect on the brain’s development. Lin et al. saw a cumulative degradation in spatial performance during the seizure days in adult rats trained at a spatial accuracy task, with reversal of the deficit after seizures were stopped. In fact, performance returned to baseline suggesting that in adult rats—with mature brains—seizures per se have a reversible damaging effect on function (3). However, when rats experienced repeated seizures in the first weeks of life, subsequent testing during adulthood showed that seizure-exposed rats had initial difficulties learning a memory task but performed similarly to controls after extra training. This demonstrates delayed but still remediable cognitive implications of early-life seizures (4). Whether there is a threshold that cannot be crossed—an early enough timing or a high enough seizure burden—for these cognitive changes to become irreversible remains to be seen. The direct translation to humans with epilepsy also remains under discussion. All in all, though, the basic premise becomes that if we subject a normal brain to seizures early in life, negative but reversible cognitive consequences occur. In the word normal lies the first caveat to the prevailing logic directly linking seizure control with resolution of cognitive deficits in childhood epilepsy, as evidence is cumulating to suggest that in humans, epilepsy and its comorbidities do not necessarily start with the first seizure.

In fact, multiple population-based studies have documented higher rates of cognitive challenges in children with epilepsy before an initial presentation with their first seizure (5). Up to 25% of children with epilepsy were already receiving special academic school services before their first recognized seizure in one study (5), and 27% of preschool aged children with just one seizure exhibited deficits on their neuropsychological testing at or near disease onset in another study (1). Similar to these cognitive comorbidities, psychiatric disorders such as depression and anxiety, as well as behavioral challenges such as attention deficit hyperactivity disorder, all precede the first seizure in many children with epilepsy—at rates that can reach up to 2 to 3 times those expected in the general population (5). Besides the obvious correlation of gross MRI structural abnormalities and a symptomatic epilepsy etiology with cognitive delays, as seen in the studies at hand for this commentary, elegant neuroimaging work in children with idiopathic epilepsy documented several abnormalities in brain development prior to onset and diagnosis of epilepsy. These include expansion of the ventricular system, especially among children with idiopathic generalized epilepsy (6), differences in baseline grey and white matter volumes, and changes extending to subcortical structures like the thalamus, cerebellum, brainstem, and pons when compared to healthy controls (7). To the extent that these antecedent structural changes contribute to cognitive deficits in children with epilepsy upon presentation, one would expect an ongoing contribution after epilepsy presentation. Are these structural changes reversible? In particular, how responsive are they to seizure control—supposedly, the only modifiable risk factor in this equation of symptomatic epilepsy etiology, high seizure-frequency, and antiepileptic drug polytherapy driving cognitive performance? The answers are mixed.

The volumetric and ventricular abnormalities seen in idiopathic epilepsies detailed earlier did not reverse or normalize with subsequent medical treatment (7, 8). Successful temporal lobe surgery in childhood did correlate with significant IQ improvement when compared to an intractable nonsurgical control, particularly when linked to cessation of antiepileptic drugs and changes in MRI-derived grey matter volume (9). The current study by Wilson et al. suggests that this improvement is enough to transition these children with intractable epilepsy from a delayed developmental trajectory to an altered one, where they achieve some developmental tasks—but not to a normal developmental path. The group helped with surgery in the Wilson et al. study would be the hypothetical equivalent of the pharmacoresistant group (identified by Berg et al.) as the one at highest risk for cognitive deficits should seizures continue. In this group, cognitive function improved but clearly did not normalize, a finding that is somewhat explained by the functional and imaging evidence already discussed—one even more easily understood if we consider that the predictors of pharmacoresistance—such as a symptomatic epilepsy etiology, a high seizure burden before diagnosis, and difficulty in early achievement of seizure control (10)—happen to be so very similar to the predictors of cognitive delay in epilepsy.
Rather than pharmacoresistance driving cognitive delay, maybe both are driven by the epilepsy substrate.

In summary, seizure control seems to be a necessary condition for optimal cognitive outcomes in children with epilepsy. Bi-directional relationships between pharmacoresistance, epilepsy, and its cognitive co-morbidities determine how sufficient it is.

by Lara Jehi, MD

References
Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.
   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.
   This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (DGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

   Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

   For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships
   Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.
# Section #1 Identifying Information

1. Today's Date: 06/13/12

2. First Name Lara Last Name Jehi Degree MD

3. Are you the Main Assigned Author? ☒ Yes ☐ No
   If no, enter your name as co-author:


5. Journal Issue you are submitting for: 13.2

# Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

<table>
<thead>
<tr>
<th>Type</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Grant</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Consulting fee or honorarium</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Support for travel to meetings for the study or other purposes</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Fees for participating in review activities such as data monitoring boards, statistical analysis, end point committees, and the like</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Payment for writing or reviewing the manuscript</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Provision of writing assistance, medicines, equipment, or administrative support.</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Other</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This means money that your institution received for your efforts on this study.
** Use this section to provide any needed explanation.
Section #3 Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

<table>
<thead>
<tr>
<th>Type of relationship (in alphabetical order)</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Board membership</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Consultancy</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Employment</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Expert testimony</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Grants/grants pending</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Payment for lectures including service on speakers bureaus</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Payment for manuscript preparation.</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Patents (planned, pending or issued)</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Royalties</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Payment for development of educational presentations</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Stock/stock options</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Travel/accommodations/meeting expenses unrelated to activities listed.**</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Other (err on the side of full disclosure)</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section #4 Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☒ No other relationships/conditions/circumstances that present a potential conflict of interest.
☐ Yes, the following relationships/conditions/circumstances are present:

Thank you for your assistance.

Epilepsy Currents Editorial Board