Neurobehavioral Comorbidities in Children With Active Epilepsy: A Population-Based Study

WHAT’S KNOWN ON THIS SUBJECT: In addition to seizures, school-aged children with epilepsy can have coexisting cognitive and behavioral difficulties, but the spectrum and prevalence of such difficulties are uncertain.

WHAT THIS STUDY ADDS: This study provides population-based data on the prevalence of common comorbid cognitive impairments and factors associated with such diagnoses in school-aged children with “active” epilepsy.

abstract

BACKGROUND: In addition to recurrent epileptic seizures, children with epilepsy can have coexisting cognitive and behavioral difficulties but the spectrum and prevalence of such difficulties are uncertain.

METHODS: The Children with Epilepsy in Sussex Schools study is a prospective, community-based study involving school-aged children (5–15 years) with active epilepsy in a defined geographical area in the United Kingdom. Participants underwent comprehensive psychological assessment, including measures of cognition, behavior, and motor functioning. Consensus neurobehavioral diagnoses were made with respect to Diagnostic and Statistical Manual, Fourth Edition-Text Revision (DSM-IV-TR) criteria.

RESULTS: A total of 85 children (74% of eligible population) were enrolled; 80% of children with active epilepsy had a DSM-IV-TR behavioral disorder and/or cognitive impairment (IQ <85). Intellectual disability (ID) (IQ <70) (40%), attention-deficit/hyperactivity disorder (ADHD) (33%), and autism spectrum disorder (ASD) (21%) were the most common neurobehavioral diagnoses. Of those who met criteria for a DSM-IV-TR behavioral disorder, only one-third had previously been diagnosed. Logistic regression revealed that seizures in the first 24 months compared with first seizures at 24 to 60 or 61+ months (odds ratio [OR] 13, 95% confidence interval 2.2–76.9; OR 21.3, 3.2–148.9) and polytherapy (OR 7.7, 1.6–36.3) were independently associated with ID and the presence of ID was associated with a diagnosis of ASD (OR 14.1, 2.3–87.1) after Bonferroni adjustment. Epilepsy-related factors did not independently predict the presence of behavioral disorders.

CONCLUSIONS: Screening for neurobehavioral comorbidities should be an integral part of management in children with “active” epilepsy. There is a need for research to identify neurobiological mechanisms underpinning neurobehavioral impairments and studies to evaluate possible treatments. Pediatrics 2014;133:e1586–e1593

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KEY WORDS
epilepsy, children, cognition, behavior, screening

ABBREVIATIONS

ADHD—attention-deficit/hyperactivity disorder
AED—antiepileptic drug
ASD—autism spectrum disorder
CHESS—Children with Epilepsy in Sussex Schools
CI—confidence interval
DCD—developmental coordination disorder
ID—intellectual disability
ILAE—International League Against Epilepsy
OR—odds ratio

Dr Reilly undertook psychological assessments and observations of all the children and was involved in consensus neurobehavioral diagnosis and statistical analysis; Dr Atkinson was involved in recruiting participants, study design, and consensus neurobehavioral diagnosis; Professor Gillberg was involved in study design and in consensus neurobehavioral diagnosis; Professor Scott was involved in study design, the statistical analysis, and manuscript review; Ms Das was involved in ILAE classification; Professor Neville was involved in study design, ILAE classification, and manuscript review; Dr Chin was involved in study design, review of medical notes, and manuscript review; Dr Aylett was involved in study design; and Ms Burch was involved in study design and manuscript review.

(Continued on last page)
Epilepsy is the most common serious neurologic disorder in childhood, with prevalence estimates of 0.5% to 1.0% of all children from birth to 16 years. Most active epilepsy cases, even in adults, are of childhood onset. Childhood-onset epilepsy is associated with negative psychosocial outcomes, especially for those with cognitive impairment or without remission. A wide spectrum of cognitive and behavioral disorders has been associated with epilepsy, and these neurobehavioral comorbidities add significantly to the burden of the condition. Previous studies suggest that behavioral difficulties are under-recognized in childhood epilepsy. The validity of screening measures for neurobehavioral disorders is uncertain in epilepsy. Therefore, the gold standard in this population is likely to be clinical diagnosis based on information from multiple sources.

Previous population-based studies focusing on neurobehavioral comorbidities in childhood epilepsy have not combined the use of disorder-specific behavioral screening measures, measures of global cognitive functioning, and expert clinical diagnosis. Furthermore, previous studies have not examined the association of epilepsy-related factors with both cognitive and behavioral impairments. The assessment of neurobehavioral comorbidities in school-aged children with epilepsy is particularly apposite, as it would not be possible to characterize younger children with respect to neurobehavioral impairments by using internationally accepted classification systems (eg, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision [DSM-IV-TR]). The aim of the Children with Epilepsy in Sussex Schools (CHESS) study was to identify the prevalence, spectrum, and risk factors for cognitive and behavioral difficulties experienced by school-aged children with active epilepsy (on 1 or more antiepileptic drug [AED] and/or had a seizure in the past year) in a defined geographical region.

METHODS

Recruitment

All children born between 1995 and 2007 with active epilepsy (on 1 or more AED and/or had a seizure in last year) and who were resident in the RH10 to RH13 postal districts of the county of West Sussex in the south of the United Kingdom between March 31, 2011, and September 30, 2012, were eligible for inclusion. Children born before 1995 or after 2007 and who did not have active epilepsy were not eligible for inclusion. The prevalence of lifetime (a history of 2 or more unprovoked epileptic seizures) and active epilepsy in the study area was calculated by using the mid-2010 population estimates of 4- to 15-year-olds (32 212) and 5- to 16-year-olds (32 617) provided by the Office of National Statistics (total mid-2010 population 202 919). The area is similar to the UK average with respect to ethnic make-up (study area: white 87%, nonwhite 13%, United Kingdom: white 86% nonwhite 14%) and a socioeconomic index (see Supplemental Table 5). As the study spanned >1 calendar year, prevalence figures were calculated by using a mean of the population (32 414.5) of 4- to 15-year-olds and 5- to 16-year-olds. At the outset of the study, the Child Health Bureau database (a computerized database) that holds medical records of all children in the region, was searched to identify children with active and lifetime epilepsy. The database was searched by using the terms “epilepsy,” “fits,” “absences,” and “seizures” under the category “diagnosis,” for children born between 1995 and 2007 in the postal districts RH10 to RH13. All pediatricians in the area were asked to inform the research team of new diagnoses of epilepsy within the study period and hospital letters about these children were reviewed to determine eligibility.

The parents/guardians of eligible children were approached by the researchers (sent a letter and/or asked in person) and asked to complete an interest form if they wished to find out about the study. All parents who returned a form were met in the child’s school or in their home by the study psychologist to discuss their child’s participation. At this informed consent meeting, the study was described in detail and parents were asked for written consent for entry of their child into the study. The child’s teacher was also given an information sheet describing the study. Anonymized information was obtained from the Child Health Bureau database on nonparticipants with active epilepsy (n = 30), including data on school placement (specialized or mainstream), whether the child had a statement of special educational needs, the presence of intellectual disability (ID), or the presence of cerebral palsy.

Assessment

Eligible children underwent psychological assessment between April 1, 2011, and November 30, 2012. Clinical information on eligible children was extracted (by PA, R.C.S., B.G.R.N., K.B.D., and R.F.M.C.) using a standardized proforma including data on current AEDs, seizures >30 minutes, investigations (MRI, EEG), and previous neurobehavioral diagnosis. Clinical, EEG, and neuroimaging data were reviewed by 2 pediatric neurologists who manage patients with epilepsy in their clinical practice (KBD and BGRN). They independently classified seizures and epilepsy syndromes proposed by the task force of the International League Against Epilepsy (ILAE) in 2010. When the assessors disagreed on the classification, conflicts were resolved by consensus.

Parents and teachers initially completed a measure of behavioral functioning with the chosen measure dependent on the child’s developmental level (Supplemental Table 6). In 2 cases, teacher data...
were not collected, as 1 child was being home-schooled and in another case the parents did not wish their child’s teachers to complete any of the measures. Previous diagnoses of neurobehavioral conditions were recorded from children’s medical notes and parental/school reports. The children then underwent comprehensive psychological assessment (Supplemental Table 6) by an educational psychologist, including measures of cognition and school achievement. Parents, teachers, and children completed screening instruments for autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), developmental coordination disorder (DCD), depression, and anxiety.

Consensus clinical diagnoses of ASD, ADHD, DCD, oppositional defiant disorder; depressive disorder; and any anxiety disorder were made with respect to relevant DSM-IV-TR9 criteria based on consensus diagnosis by study psychologist (C.R.), pediatrician (P.A.), and child and adolescent psychiatrist (C.G.) (Supplemental Table 7). The consensus diagnostic process involved a review of children’s developmental/medical history based on case/medical notes, results of administered standardized screening measures and cognitive assessments, and school-based observations by study psychologist. Cognitive status was determined by results of tests of global cognitive functioning and participants were classified into 3 categories: normal (IQ >85), borderline (IQ 70–84), and ID (IQ <70).

Ethics Approval
The study was approved by the Brighton and Sussex Research Ethics Committee and was registered with the collaborating hospital primary care organization: The Sussex Community NHS Trust.

Statistical Methods
All analyses were done with IBM SPSS version 21.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY). χ² analyses were carried out to compare the characteristics of the participants and nonparticipants. Logistic regression analyses were done to identify the factors associated with clinical diagnoses of DSM-IV-TR9 neurobehavioral disorders. Because of the small numbers diagnosed with depression, this factor was combined with anxiety to create the category “emotional disorder” and univariable and multivariable analyses were carried out to identify factors associated with anxiety and the new category of emotional disorder. The factors included as possible predictors in the univariable analyses were ethnicity (white versus nonwhite), gender (male versus female), age of onset of first seizure (0–23 months, 24–60 months, 60+ months), duration of epilepsy (<4 years, 4–7 years, 8 years +), seizure frequency (weekly/more often, monthly/yearly, none in past year), current treatment (1 AED [monotherapy] vs 2 AEDs or more [polytherapy]). Predominant seizure type was either generalized or focal. Etiology was based on ILAE 2010–suggested classification (genetic, structural/metabolic, unknown/undetermined). DSM-IV-TR9 disorders (ASD, ADHD, DCD, depression, and anxiety) and ID were included as present/absent. Status epilepticus (seizures lasting >30 minutes) was entered as present/absent. For the diagnosis of ID, depression and anxiety were excluded as possible predictors, as none of the individuals with ID had these diagnoses and likewise ID was excluded as a possible predictor of anxiety and emotional disorder. In the first instance, all independent variables were tested by logistic regression. Multivariable analysis was carried out by backward (conditional) regression, with all predictors entered into the model to identify factors independently associated with the outcome variables. In the multivariable analysis, the following variables were entered as the reference variables in predictors with >2 categories: duration (8 years +), frequency (weekly/more often), age category of first seizure (0–24 months), and etiology (unknown/undetermined). The α level for univariable and multivariable analysis was P < .05. Results of the multivariable analyses are reported before and after Bonferroni adjustment for multiple comparisons (α level of adjustment was P < .008).

RESULTS
This initial search, using the Child Health Database, yielded 202 children (Fig 1). The medical files of all these children were reviewed by a community pediatrician (PA.), and 8 children were determined not to have had lifetime epilepsy and 1 was deemed not to be living in the study area, resulting in 193 children. During the study period, 5 further children were diagnosed with epilepsy and were eligible for inclusion. Of the 198 children with lifetime epilepsy, 115 were deemed to have active epilepsy and were thus eligible for participation during the study period (Fig 1). Of the 115 parents with eligible children, 88 returned interest forms indicating an interest in participating in the study and 85 (74%) participants underwent initial screening and subsequent psychological assessment (Fig 1). The prevalence of lifetime epilepsy was 6.1 (95% confidence interval [CI] 5.2–6.9) per 1000 (1 in 175) and prevalence of active epilepsy was 3.5 (95% CI 3.0–4.3) per 1000 (1 in 286). Statistically significant differences between the participants (n = 85) and nonparticipants (n = 30) with active epilepsy were not noted except for gender (P < .05) (Supplemental Table 8), indicating that nonparticipants and participants were likely to be similar with respect to neurobehavioral impairment. The main characteristics of the children who participated in the CHESS study are shown in Table 1 (further details in Supplemental Table 9).

Figure 2 illustrates the number of children who met DSM-IV-TR9 diagnostic
criteria in the current study for a behavioral disorder and those previously diagnosed with behavioral conditions. All children previously diagnosed with a specific DSM-IV-TR disorder met current criteria for the disorder. The most common behavioral diagnosis was ADHD (33%), followed by ASD (21%), and DCD (18%). Of the 60% of children who met diagnostic criteria for a DSM-IV-TR disorder, only one-third had previously been diagnosed. With respect to cognitive functioning, 40% were functioning in the ID (IQ <70) range, 15% in the “borderline” intellectual functioning (IQ70–84), and 45% in the “normal” (IQ >85) range. Table 2 illustrates the number of children who met diagnostic criteria for one or more DSM-IV-TR disorder and/or cognitive impairment (IQ <85); 80% of children had cognitive impairment and/or at least one DSM-IV-TR disorder, 34% had cognitive impairment and at least one behavioral disorder, and 26% of children met criteria for ≥2 DSM-IV-TR behavioral disorders.

The factors significantly associated with ID are shown in Table 3. Nonwhite ethnicity, weekly seizures versus monthly/yearly seizures and versus no seizures in past year, and duration of ≥8 years versus <4 years were significantly associated with ID on univariable analysis only. On multivariable analysis, the following were independent predictors of having ID: first seizures before 24 months compared

FIGURE 1
Participant recruitment in CHESS study.
TABLE 1 Characteristics of Participants in the CHESS Study (n = 85)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender male/female</td>
<td>44/41 (52/48)</td>
</tr>
<tr>
<td>Ethnicity white/nonwhite</td>
<td>65 (76)/20 (24)</td>
</tr>
<tr>
<td>Attending a special school</td>
<td>42 (49)</td>
</tr>
<tr>
<td>On special educational needs register</td>
<td>61 (72)</td>
</tr>
<tr>
<td>Special Educational Needs†</td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>46 (54)</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>15 (18)</td>
</tr>
<tr>
<td>Mean duration of epilepsy (range)</td>
<td>5.83 y (0.24–15.32)</td>
</tr>
<tr>
<td>Mean age at time of psychological assessment (range)</td>
<td>10.79 y (5.08–15.75)</td>
</tr>
<tr>
<td>Age of seizure onset, mo</td>
<td></td>
</tr>
<tr>
<td>0–24</td>
<td>26 (31)</td>
</tr>
<tr>
<td>25–80</td>
<td>28 (33)</td>
</tr>
<tr>
<td>61+</td>
<td>31 (38)</td>
</tr>
<tr>
<td>EEG</td>
<td>85 (100)</td>
</tr>
<tr>
<td>Seizures 30 min or longer</td>
<td>22 (26)</td>
</tr>
<tr>
<td>Current seizure frequency‡</td>
<td></td>
</tr>
<tr>
<td>Weekly or more often</td>
<td>32 (38)</td>
</tr>
<tr>
<td>Monthly/yearly</td>
<td>38 (45)</td>
</tr>
<tr>
<td>None in past year</td>
<td>15 (18)</td>
</tr>
<tr>
<td>Number of current AEDs</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4 (5)</td>
</tr>
<tr>
<td>1</td>
<td>51 (60)</td>
</tr>
<tr>
<td>2</td>
<td>22 (26)</td>
</tr>
<tr>
<td>3</td>
<td>8 (9)</td>
</tr>
<tr>
<td>ILAE 2010 predominant seizure type†</td>
<td></td>
</tr>
<tr>
<td>Generalized</td>
<td>28 (33)</td>
</tr>
<tr>
<td>Focal</td>
<td>57 (67)</td>
</tr>
<tr>
<td>Epileptic spasms</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Tonic-clonic</td>
<td>20 (24)</td>
</tr>
<tr>
<td>Absence</td>
<td>22 (26)</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>13 (15)</td>
</tr>
<tr>
<td>Clonic</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Tonic</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Atonic</td>
<td>9 (11)</td>
</tr>
<tr>
<td>ILAE 2010 etiology‡</td>
<td></td>
</tr>
<tr>
<td>Genetic/presumed genetic</td>
<td>32 (38)</td>
</tr>
<tr>
<td>Structural/metabolic</td>
<td>26 (31)</td>
</tr>
<tr>
<td>Unknown/undetermined</td>
<td>27 (32)</td>
</tr>
</tbody>
</table>

All data based on a review of medical notes unless otherwise indicated. All values are n (%) unless otherwise noted.

† In the United Kingdom, a Statement of Special Educational Needs is a legal document that sets out a child’s special educational needs as assessed by the Local Education Authority. It sets out the educational provision that the authority feels a child needs. Most children on the special educational needs register will not have a statement, as it is reserved for children with the greatest level of need.

‡ Data based on parental report.

§ All participants were classified with respect to predominant seizure type (ie, generalized or focal) based on initial classification. Epileptic spasms were included in the generalized group.

with onset at 24 to 60 and onset at 60+ months, being on polytherapy, having ASD, having predominantly generalized seizures, and having experienced at least 1 episode of status epilepticus. After Bonferroni correction, the presence of ASD, having predominantly generalized seizures, and having experienced status epilepticus no longer remained significant.

The factors significantly (P < .05) associated with DSM-IV-TR® neurobehavioral disorders are shown in Table 4. For a diagnosis of ASD, duration of ≥8 years versus <4 years, and predominately generalized seizures were significantly associated with ASD on univariable but not multivariable analysis. On multivariable analysis, the presence of ID and unknown/undetermined etiology were independent predictors of having ASD. The presence of DCD was the only factor significantly associated with ADHD on univariable and multivariable analysis. The presence of ADHD was associated with a diagnosis of DCD on univariable analysis but not multivariable analysis. Unknown/undetermined etiology as opposed to structural/metabolic etiology was independently associated with a diagnosis of DCD. The presence of depression was the only significant predictor of anxiety on univariable and multivariable analysis. None of the predictors were associated with a diagnosis of an emotional disorder. After Bonferroni correction, the only associations that remained significant were the presence of ID and unknown/undetermined etiology as significant predictors of ASD.

DISCUSSION

The results of this study provide population-based data on neurobehavioral comorbidity in children with active epilepsy and add significantly to knowledge of the prevalence and spectrum of neurobehavioral comorbidity in the condition. This group of children have a high rate of neurobehavioral comorbidity and often have difficulties across a range of domains. The difficulties across a range of domains likely reflects the impact of underlying etiology and/or epileptic activity across maturing neuronal networks and pathologic interactions between brain areas. Only one-third of children who met criteria for at least 1 DSM-IV-TR® disorder had previously been diagnosed. The reasons for this underrecognition may be because of the low number of children assessed by mental health professionals and thus may indicate either a lack of recognition of need for referral or lack of appropriate services to meet this particular need. In the former case, it may be that children with epilepsy are subject to a form of “diagnostic overshadowing,” with the neurologic disorder overshadowing neurobehavioral symptoms.
The rate of ID and DSM-IV-TR disorders is higher than previous population-based studies of cognition and behavior, likely reflecting the fact that the previous studies focused on lifetime or parent-reported epilepsy as opposed to active epilepsy. Children with “current” epilepsy have been reported to have higher rates of behavioral disorders than children with lifetime epilepsy. In this study, factors independently associated with ID included having experienced seizures before 24 months, polytherapy, generalized seizures, ASD, and status epilepticus. The relationship between early-onset seizures and poor cognitive outcome has previously been noted in a number of population-based studies. The use of polytherapy and negative cognitive outcome has also been noted and probably reflects a need to try to treat drug-resistant seizures. The association with ID and “predominantly generalized” seizures suggests that seizures affecting the whole of the brain may be more deleterious compared with focal seizures, which may be associated with more selective cognitive impairments, and poorer global cognitive outcome has been associated with presence of generalized seizures. The association between ASD and ID in epilepsy has been well documented and may reflect common underlying pathophysiological mechanisms. The relationship between status epilepticus and unfavorable neurodevelopmental outcome has previously been noted, although premorbid abilities may eclipse the direct effects of status epilepticus on outcome. It is important to note that the analyses have identified associations that may or may not be causative. The nature and severity of specific underlying brain abnormalities were not captured with our approach, and it is likely that these factors will have an important influence on the outcome of some of the predictors and on the outcome itself.

Epilepsy-related factors (e.g., age of onset, seizure frequency) were in the main not

TABLE 2 Neurobehavioral Comorbidity in the CHESS Study

<table>
<thead>
<tr>
<th>Total Population, n = 85, n (%)</th>
</tr>
</thead>
</table>
| Number with 0 DSM-IV-TR disorder | 34 (40)  
| Number with 1 DSM-IV-TR disorder | 28 (33)  
| Number with 2 DSM-IV-TR disorders | 16 (19)  
| Number with 3 DSM-IV-TR disorders | 5 (6)  
| Number with 4 DSM-IV-TR disorders | 1 (1)  
| ID (IQ < 70) | 34 (40)  
| Cognitive impairment (IQ < 85) | 47 (55)  
| At least 1 DSM-IV-TR diagnosis and/or or cognitive impairment | 68 (80)  
| Cognitive impairment and at least 1 DSM-IV-TR disorder | 29 (34)  

Note: Not including ID.
Emotional disorders Nothing significant

Anxiety Depression (50%) versus nondepression (10%) 8.875 (1.528)

ADHD DCD (32%) versus non-ADHD (12%) 3.383 (1.104)

ADHD DCD (56%) versus non-DCD (28%) 3.383 (1.104)

ADHD and DCD) also have been noted in a number of children who reach criteria for DSM-IV-TR disorders. DCD, developmental coordination disorder; ADHD, attention-deficit/hyperactivity disorder.

Percentages indicate the proportion of children who met criteria for DSM-IV-TR disorders. DCD, developmental coordination disorder; ADHD, attention-deficit/hyperactivity disorder.

**CONCLUSIONS**

Given the high rate of neurobehavioral comorbidity in childhood epilepsy and noted underrecognition, screening of all children for cognitive and behavioral difficulties would seem warranted, as has been previously recommended. The lack of association between epilepsy variables and behavioral problems suggests that many children’s difficulties are not caused by seizures per se but by other biological factors responsible for both seizures and neurobehavioral difficulties and/or psychosocial factors. Although there have been limited studies on interventions to treat/manage behavioral comorbidities in childhood epilepsy, studies that have been carried out suggest a good response. Therefore, identification of such difficulties should be an integral part of management in childhood epilepsy. With respect to cognitive impairments in childhood epilepsy, there is an urgent need to develop an enhanced understanding of the neurobiological basis of the impairments, as such an understanding is likely to lead to the development of behavioral or pharmacological treatments that may improve cognitive outcome and also impact positively on behavioral comorbidities.

An increased understanding of the neurobiological basis of the neurobehavioral impairments of childhood epilepsy is likely to be garnered by prospective studies focusing on mechanisms responsible for impairments before and after the appearance of overt seizures.

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