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Psychiatric disorders and suicidal behavior in neurotypical young adults with childhood-onset epilepsy

Elisa Baldin, MS MD[1], **Dale C Hesdorffer, PhD**[1], **Rochelle Caplan, MD**[3], and **Anne T. Berg, PhD**[4]

[1]Columbia University, GH Sergievsky Center and Department of Epidemiology, New York, NY, USA

[3]University of California at Los Angeles, David Geffen School of Medicine, Semel Institute of Neuroscience and Human Behavior, USA

[4]Epilepsy Center, Ann & Robert H Lurie Children's Hospital of Chicago, Department of Pediatrics, Northwestern Feinberg School of Medicine, Chicago IL, USA

Abstract

OBJECTIVES—We examined the association between lifetime, current history of psychiatric disorders, suicidal thoughts and behaviors with childhood-onset epilepsies in a community-based cohort of young adults.

METHODS—Cases were neurotypical (normal neurological, cognitive, and imaging exams and no evidence of a brain insult responsible for the epilepsy) young adults with childhood-onset epilepsy followed since the onset of their epilepsy approximately 15 years earlier and recruited as part of a community-based study. They were compared to two different control groups, siblings and external controls from the National Comorbidity Survey-Replication (NCS-R). The Diagnostic Interview Survey assessed lifetime and current DSM-IV-TR diagnoses of mood disorders and anxiety disorders. Suicidal thoughts and suicide attempt were assessed using the Diagnostic Interview Survey for Children-IV and the Diagnostic Interview Survey.

RESULTS—Two hundred fifty-seven cases and 134 sibling controls participated in the DIS portion of the young adult assessment. Comparing cases both to their sibling controls and to the controls drawn from the NCS-R, we did not find any evidence to suggest a higher prevalence of lifetime and current mood or anxiety disorders, suicidal thoughts and suicide attempt in young adults with childhood-onset epilepsies.

SIGNIFICANCE—Our findings, from a community-based sample of neurotypical young adults, do not suggest a substantial or lasting association between childhood epilepsy and psychiatric disorders and suicidal behavior.

Address for correspondence: Anne T. Berg, PhD, Epilepsy Center, Lurie Children's Hospital, 225 East Chicago Ave, Box 29, Chicago, IL, atberg@luriechildrens.org.

Conflict of interest:
None of the authors has any conflict of interest to disclose.

Keywords

Epilepsy; psychiatric disorders; case-control study

INTRODUCTION

The relation between childhood epilepsy and various behavioral and psychiatric disorders has been repeatedly discussed in the literature for well-over 50 years.[1–3] Reasons have included inappropriate reactions on the parts of others leading to stigmatization and the response of the children to that stigma[1, 2] as well as underlying brain insults which may produce a range of cognitive and psychiatric disorders, as well as seizures.

There is a hypothesis that shared mechanisms of epilepsy and psychiatric disorders might affect otherwise neurologically typical individuals and that psychiatric disorders and epilepsy are part of a larger spectrum of brain disorders with shared mechanisms. This has been suggested by studies reporting a higher prevalence of psychiatric disorders in children with epilepsy relative to control children. [4–7]

We examined this hypothesis within a community-based cohort of young adults who had originally been identified at the time of their initial diagnosis of epilepsy and then followed prospectively since then.

METHODS

Subjects with newly-diagnosed childhood-onset epilepsy (N=613) were recruited from the offices of pediatric neurologists, pediatricians and adult neurologists throughout the state of Connecticut from 1993–1997.[8] Parents were interviewed and contacted every 3–4 months to ascertain the occurrence of further seizures, changes in medications and additional information. At 8–9 years after initial study entry, 502 children and their parents (83.4%) participated in a comprehensive reassessment protocol, although one was later excluded for confidential reasons. A formal neuropsychological testing was also provided for research purposes in 66.7% (335) of the cases. The remaining subjects had detailed information on schooling, education diagnoses, related medical diagnoses, as well as the results of any neuropsychological testing done by the school systems or for other medical reasons. [9] For the 9-year assessment, 285 sibling controls were recruited, and the same instruments were administered.

Approximately 7–8 years later (~15 years after recruitment), those neurotypical cases (normal neurological exam, absence of intellectual disability, normal imaging, and no evidence or history of an underlying brain insult or related condition that could explain the epilepsy) who attained the age of majority and agreed to participate underwent a young adult assessment. Parents of case participants <18 years of age consented for the new assessment with the assent of their children. Two experienced interviewers administered the Diagnostic Interview Survey (DIS-IV) by phone to assess lifetime DSM-IV-TR diagnoses of mood and anxiety disorders.[10, 11] These interviewers participated in a one week DIS training, focused on the standardized interview, prior to initiating the 15 year assessment. Suicidal thoughts

and behaviors (i.e. attempts) were also assessed using the Diagnostic Interview Survey for Children (DISC-IV). The DIS has moderate to excellent reliably (Kappa ≥ 0.50) for all disorders we studied. [11]

Two controls groups were employed. We invited the same controls that participated in the previous 9-year assessment.[12] In addition, we constructed an external group drawn from the National Comorbidity Survey-Replication (NCS-R) dataset,[13] whose data were obtained, with permission, from the NCS_R website. The NCS-R is a US nationally representative household survey of subjects aged 18 years and older that assessed diagnoses of DSM-IV-TR disorders using the Composite International Diagnostic Interview, which was formulated based upon the DIS-IV.[13] The response rate was 70.9%. We randomly sampled the NCS-R controls by age group (18–25, 25–30, 30–35) at a ratio of 3 controls for each case with epilepsy. We used the additional control group because psychiatric disorders tend to cluster in families which could lead to over-matching and obscuring of positive association when sibling controls are used. [14–17]

This study was approved by the institutional review boards of Yale University, Lurie Children's Hospital and Columbia University. Each patient's parent or guardian provided written informed consent and a written assent from the patient was obtained when appropriate. As study subjects reached the age of majority a written consent was then provided.

Psychiatric disorders

We assessed lifetime and current anxiety and mood disorders by means of the DIS-IV diagnoses in both cases and sibling controls. Suicidal thoughts and behaviors were also assessed with the suicidality module of the DISC [10] and the depression module of the DIS-IV.

Lifetime anxiety disorder included generalized anxiety disorder, panic disorder with and without agoraphobia, agoraphobia, agoraphobia without panic disorder, social phobia, and specific phobia.

Current anxiety disorder included generalized anxiety disorder in the previous year, panic disorder with or without agoraphobia in the previous year, agoraphobia without panic disorder in the previous year, social phobia in the previous year.

Lifetime mood disorder included major depressive episode, major depressive disorder single episode, major depressive disorder recurrent, depressive episode with melancholic features, bipolar I disorder, bipolar II disorder, bipolar I disorder single manic episode, dysthymic disorder, manic episode, mixed episode, hypomanic episode.

Current mood disorder included major depressive episode in the previous year, dysthymic disorder in the previous year, manic episode in the previous year, hypomanic episode in the previous year.

Suicidal thoughts and behaviors Suicidal thoughts including plans and suicide attempt were reported on either the DISC-IV [18] or the depression section of DIS-IV. Suicide attempt was defined as a positively endorsing a question on the suicidality module of the DISC-IV.

Statistical analysis

We used frequencies and percentages to summarize categorical variables, and medians and interquartile ranges for continuous variables. The distributions of the factors between cases and controls were compared using $\chi 2$ test for categorical variables and Wilcoxon's test (or t-test) for continuous variables.

Multivariable analyses—Multiple logistic regression was used to examine the association, as measured by the odds ratio, between epilepsy and psychiatric disorders as well as suicidal thoughts and behaviors. Adjustment was made for gender and age at the young adult assessment in all analyses. Three parallel analyses were performed: (a) an unmatched case-sibling control analysis; a matched case-sibling control analysis; a case-external (NCS-R) control analysis.

All statistical analyses were conducted using SAS Version 9.2(SAS Institute, Cary, NC, USA).

RESULTS

Two hundred fifty-seven cases and 134 sibling controls participated in the DIS portion of the young adult assessment. This represents 66% of neurotypical cases who participated in the 9-year assessment. All but 15 (5.8%) in our DIS sample had neuroimaging (5 had a genetic generalized epilepsy, e.g. CAE, 3 BECTS, 7 nonsyndromic epilepsies). We were not able to contact controls if their case did not participate in the young adult assessment; however, of cases who participated in the DIS and who had a control at the 9-year assessment, 78% had a control participate in the DIS as well. The mean age at onset of epilepsy was 6.2 (SD 3.9, range: 0.08–15.6) years. The mean age at interview was 22.5 (SD 3.5, range: 16.5–32.8) years for cases and 23.6 (SD 5, range: 15.6–46.6) years for controls. Among cases, 15 (23.4%) subjects on medication were in 5-year remission, and 181 (94.3%) of those off medications were in 5-year remission (Table 1). The types of epilepsy in the sample excluded more severe epilepsies such as West or Lennox-Gastaut syndrome as those epilepsies rarely occur in neurotypical individuals. The other syndromes, Benign Epilepsy with Centro-temporal Spikes (BECTS), Childhood Absence Epilepsy (CAE), and Juvenile Absence and Juvenile Myoclonic Epilepsies (JAE&JME) are some of the most common electro-clinical childhood syndromes and accounted for nearly 40% of this sample of young adults with uncomplicated childhood epilepsy. The distribution of psychiatric disorders did not differ substantially across these syndromes and nonsyndromic epilepsies (Supplemental Table 1). There were a few unexpected associations between AED use and mood disorders (specifically in patients in remission) and between current AED use and history of suicide attempt Supplemental Table 2).

Differential participation in the DIS

There was no differential participation in the DIS-IV for cases in the young adult assessment according to the presence or absence of remission at the 9-year assessment (participation was 66.3% for cases in remission at 9 years vs 61.9% not in remission; p=0.9). We also found no evidence of differential DIS participation in cases and controls as a function of reported depression at the 9-year assessment. Within the uncomplicated cases, 62% of those reporting depression at 9-years versus 66% not reporting depression participated in the DIS at 15 years (p=0.54). The comparable figures for the controls who participated in the 9-year assessment were 60% and 58% (p=0.80).

(a) Cases versus sibling controls: unmatched analysis

Lifetime mood disorders were present in 53 (20.6%) cases and 31 (23.1%) sibling controls (p=0.6). Lifetime anxiety disorders were present in 40 (15.6%) cases and 27 (20.2%) sibling controls (p=0.3) (Table 2).

Current mood disorders were present in 33 (12.8%) cases and 16 (11.9%) sibling controls (p=0.8). Current anxiety disorders were present in 16 (6.3%) cases and 11 (8.4%) sibling controls (p=0.5) (Table 2).

After adjustment for age at interview and gender, the association between epilepsy and lifetime or current DSM-IV-TR diagnoses of mood disorder or anxiety disorder was not statistically significant and the odds ratio was close to the null value of 1.0 (Table 3). The odds ratio for epilepsy and suicide attempt was 2.5 (p=0.2).

(b) Matched case-sibling control analyses

Matched analyses were consistent with the unmatched analysis but numbers were smaller and there were not statistically significant associations (Table 3).

(c) Cases and NCS-R controls

Compared to controls drawn from the NCS-R, lifetime and current anxiety disorders were associated with a significantly decreased odds of epilepsy. No other psychiatric disorders or suicidal thoughts and behaviors were related to epilepsy (Table 3).

DISCUSSION

To our knowledge, this is the first community-based study of childhood-onset epilepsy in which DSM-IV-TR lifetime and current psychiatric disorders were assessed once children reached young adulthood. We found little relationship between psychiatric diagnoses and childhood-onset epilepsy in neurotypical young adults in comparison to sibling controls. Because the use of sibling controls could potentially obscure an association due to the observed familial aggregation of behavioral and psychiatric disorders,[14, 15] we also used a separate control group drawn from a survey conducted in the general population.[13] This comparison, too, did not reveal any evidence of an increased life-time prevalence of psychiatric disorders in our case group.

At first glance, our results appear to differ from what might be expected based on cross-sectional studies that have shown associations between psychiatric disorders and childhood onset epilepsy in both clinical[4, 5, 19] and population-based studies [7, 20, 21] of prevalent epilepsy. On further consideration, however, it becomes clear that the subject is more complex. Factors relating to the study design and sampling require careful attention.

The two studies that have most recently and most specifically demonstrated an association between epilepsy and various psychiatric disorders based on psychiatric assessments of the children themselves included case children either exclusively or largely from tertiary centers. In one series[4] 152 children with active epilepsy were selected for having at least 1 seizure in the previous year; half had >10 seizures per year. Almost all were on medications. They were studied at an average age of about 10 years-old. Further, controls with known psychiatric diagnoses were excluded from the study. The second study[5] recruited 53 recently-diagnosed children from two tertiary centers and assessed them during the first year after diagnosis. The targeting and recruitment of the children into that series is not described; however most children were on medications and all had had recent seizures. A third study from the UK was a population-based[7] study and reported on 42 children with uncomplicated epilepsy (average age 10 years, maximum 15 years at the time of the assessment). Information for children under 11 years (over half the series) came primarily from parent interviews. These scenarios contrast with ours in many respects. First, our cases were sampled on a state-wide (near population) basis at the time of initial diagnosis. Second, most of our cases were seizure-free for many years and off medication at the time they were assessed.[22] Finally, our cases and controls were assessed at 22–23 years of age on average, about twice as old as the children in the other studies although the ages at onset of epilepsy were similar.

There has been concern that the often intertwined psychosocial and psychiatric impact of epilepsy might persist into adulthood. Analyses from recent longitudinal studies, however, have raised questions about the long-term persistence of that impact, especially in patients for whom the epilepsy is resolved.[23–25] For example, young adults with a history of BECTS or resolved focal seizures do not appear to be disadvantaged by having had epilepsy in childhood.[23, 24] These studies did not assess psychiatric diagnoses per se; however, they do suggest better social outcomes than have been reported from older cohort studies[26, 27] Of note, finding of an association between current AED use and history of past suicide attempt as well as the finding that the small number of cases subjects in remission but still on AEDs had a relatively high likelihood of mood disorders (current and past) were both based on *post hoc* comparisons and were unexpected. We do not know for certain but suspect that the medications (AEDs) may have been used as treatment for mood and related disorders.

A potential source of bias in our study comes from loss to follow-up over time and the concern that individuals with psychiatric disorders might be less inclined to participate in a psychiatric interview such as the DIS than those without. The best measure we had and which was collected in the same way for cases and controls, was parent- or self-reported depression at the 9-year assessment. There was no evidence to suggest differential participation (and hence bias) as the 9-year reported depression was not associated with later DIS participation for either cases or controls. Of note, previous analyses from our cohort

based on this 9-year self/parent-reported diagnoses of depression obtained when participants were on average 15 years-old also did not find any suggestion of an increased prevalence of depression in cases compared to their sibling controls.[12]

An assumption in using a self-report measure of life-long psychiatric symptoms to determine past psychiatric diagnoses is that these symptoms can be reliably remembered from childhood and reported in young adults. This may not be a valid assumption, and the reported histories may under-ascertain previous psychopathology, although we would expect this to be true in controls as well. Regardless, appropriate vigilance to the psychosocial and psychiatric difficulties children with active epilepsy face, at the time of diagnosis and during the active course of their epilepsy, is most certainly warranted. Another factor that has changed over time and which varies across settings concerns the societal attitudes toward people with epilepsy and the resources available to them, particularly special educational services. The neurotypical patients in our study,[28] were the recipients of considerable special educational resources both before and after the diagnosis of their epilepsy.[29] One can speculate as to whether this earlier intervention resulted in somewhat better psychosocial, including psychiatric, outcomes than have been seen in older studies. These caveats aside, our study does suggest, that on the whole, otherwise neurotypical young adults with childhood-onset epilepsy, most of whom have epilepsy that is completely resolved, do not carry an excess mental health burden into adulthood.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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KEY POINTS

- Psychiatric disorders in neurotypical young adults with prior childhood epilepsy are no more common than in controls.
- The reliability of young adults to report psychiatric conditions from childhood is unknown.
- Secular factors including increased special school services and changing attitudes may help lessen burdens associated with epilepsy.

Table 1

Demographics for uncomplicated cases and sibling controls

Factors	Uncomplicated Cases	Controls
	N (%)	N (%)
Number	**257**	**134**
Gender (male)		
N (%)	131(51)	55 (41)
Age at onset		
Mean (SD)	6.2 (4.1)	NA
Median (IQR)	6.0 (3.0–8.6)	
Age at interview		
Mean (SD)	22.5 (3.5)[1]	23.6 (5)
Median (IQR)	21.7 (19.6–24.7)	22.4 (19.9–26.6)
Syndrome		
BECTS+[2]	38 (14.8)	NA
CAE	42 (16.3)	
JAME	19 (7.4)	
Other	158 (61.5)	
Proportion in 5-year remission		
On medication (N=64)	15 (23.4)	NA
Off medication (N=193)	182 (94.3)	

[1] p=0.02, uncomplicated cases vs. controls;

[2] BECTS+ = predominantly Benign Epilepsy with Centro-Temporal Spikes but contains and related forms of epilepsy such as Panayiotopoulous syndrome

CAE = Childhood Absence Epilepsy
JA/ME Juvenile Absence or Juvenile Myoclonic Epilepsy

Table 2

Distribution of psychiatric disorders and suicidality in all cases and sibling controls.

	Cases N=257	Controls N=134	NCS-R controls N=771
DIS lifetime			
Mood disorder	53 (20.6)	31 (23.1)	184 (23.9)
Anxiety disorder	40 (15.6)	27 (20.2)	214 (27.8)
DIS current			
Mood disorders	33 (12.8)	16 (11.9)	104 (13.5)
Anxiety disorder	16 (6.3)[1]	11 (8.4)[2]	112 (14.5)
DISC			
Suicide ideation	41 (16)	18 (13.4)	101 (13.1)
Suicide attempt	13 (5.1)	3 (2.2)	28 (3.6)

DIS – diagnostic interview survey; DISC – Diagnostic interview survey for children

[1] missing information on 4 cases: 3 subjects indeterminate current agoraphobia without panic disorder, 1 subject indeterminate current social phobia;

[2] missing information on 3 controls: 3 subjects indeterminate current agoraphobia without panic disorder.

Table 3

Adjusted odds ratios for psychiatric disorders and suicidal thoughts and behaviors in uncomplicated cases compared to sibling controls and to NCS-R controls

Factors	Unmatched adjusted OR[1] (257 uncomplicated cases, 134 sibling controls)	Matched adjusted OR (134 case-sibling control pairs)	Unmatched adjusted OR[1] (257 cases, 771 NCS-R controls)
Psychiatric disorders			
Mood disorder	0.9 (0.6–1.6), p=0.8	0.8 (0.4–1.7), p=0.6	0.8 (0.6–1.2), p=0.3
Anxiety disorder	0.9 (0.5–1.5), p=0.6	0.7 (0.3–1.4), p=0.3	0.5 (0.3–0.7), p= 0.0003
Current Mood disorder	1.2 (0.6–2.3), p=0.6	1.3 (0.6–2.8), p=0.4	0.9 (0.6–1.4), p=0.7
Current anxiety disorder	0.8 (0.4–1.8)[2], p=0.6	0.9 (0.4–2.5)[3], p=0.9	0.4 (0.2–0.7)[4], p=0.002
Suicidal thoughts and behaviors			
Suicidal ideation	1.2 (0.7–2.3), p=0.5	1.0 (0.4–2.3), p=0.95	1.3 (0.9–1.9), p=0.2
Suicide attempt	2.5 (0.7–9.4), p=0.2	3.8 (0.6–24.7), p=0.2	1.4 (0.7–2.8), p=0.3

[1] adjusted for age at the young adult year interview and gender;

[2] missing information on 4 cases: 3 subjects indeterminate current agoraphobia without panic disorder, 1 subject indeterminate current social phobia; 3 controls: indeterminate current agoraphobia without panic disorder.

[3] missing information on 1 case: indeterminate current social phobia, and on 3 controls: indeterminate current agoraphobia without panic disorder.

[4] missing information on 4 cases: 3 subjects indeterminate current agoraphobia without panic disorder, 1 subject indeterminate current social phobia;