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Parental report of behavioral and cognitive diagnoses in childhood-onset epilepsy: a case-sibling-controlled analysis

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Abstract

Evidence from multiple sources has highlighted the increased burden of cognitive, behavioral, and psychiatric disorders in childhood-onset epilepsy. Some of this increased morbidity, however, is attributable to underlying structural and metabolic insults. We assessed whether cognitive/behavioral/psychiatric disorders were associated with epilepsy of unknown or presumed genetic cause in young people with epilepsy (cases) compared to sibling controls. Our analyses included 217 cases who were enrolled in the Connecticut Study of Epilepsy between 1993 and 1997 and 217 sibling controls. Information was collected from a parent interview conducted 8-9 years after the case was diagnosed with epilepsy. Compared to controls, parents were more likely to report that their case children were slow learners (OR=4.6, $p<0.001$), had a language disorder (OR=5.8, $p<0.001$), and had engaged in self-injurious behaviors other than suicide attempts (OR=5.5, $p=0.013$). Future research should examine whether these conditions first present during childhood influence prognosis into adulthood.

Keywords

Childhood-onset epilepsy; cognitive; behavioral; psychiatric; disorders; epidemiology

Introduction

A growing body of literature has demonstrated an increased level of a variety of cognitive, behavioral, and psychiatric (CBP) disorders in people with epilepsy [1-8]. Some of these

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studies, however, have included patients with clear evidence of structural or metabolic causes for their epilepsy [3,4,6]. Methods for selecting controls groups have also varied with some studies using classmate controls [5], others population-based controls [3,4], others using children from community schools who did not have prior neurologic disorders, language disorders, or hearing disorders or psychiatric diagnosis or treatment [1,2]. One study used first degree cousins [6], and one used sibling controls although that particular study also included a small proportion of case children with structural brain lesions [9]. Each design provides critical information about different aspects of the association between epilepsy and various cognitive and behavioral disorders. Our approach focuses on children without structural-metabolic causes for their epilepsy and compares them to sibling controls. This can isolate the effects of epilepsy from those of underlying structural lesions and control for familial-genetic factors and school environment, which can impact cognitive and behavioral problems.

Our aim was two-fold. First, we examined parental report of cognitive, behavioral, and psychiatric diagnoses in young people with epilepsy without evidence of structural brain abnormalities (cases) versus their sibling controls in a prospective community-based study of children identified at their diagnosis of epilepsy. Second, we explored whether seizure remission status and age at onset influenced the odds of having a cognitive/behavioral/psychiatric (CBP) impairment.

Methods

Study Cohort

613 children with newly diagnosed epilepsy were prospectively identified by pediatric neurologists, pediatricians, and adult neurologists in the state of Connecticut and recruited into the Connecticut Study of Epilepsy between 1993 and 1997 [10]. Parents initially completed a questionnaire which included items on developmental, learning, behavioral and psychiatric disorders, and chronic medical conditions. At 8-9 years after the diagnosis of epilepsy, cases were invited to participate in a reassessment protocol which included a parental questionnaire, neurocognitive testing, and an MRI. Of the original 613 children in the cohort, 502 (81.9%) participated in the questionnaire portion of the reassessment. This represented 94.7% of those actively followed at the time of the assessment. Sibling controls were available and obtained for 285 cases. Analyses are limited to 217 pairs for which the case did not have a known structural or metabolic underlying cause and did not have an electro-clinical syndrome that could be characterized as an epileptic encephalopathy (epilepsy of unknown or presumed genetic cause) [11,12].

Demographics

Among cases, we considered the age at onset of epilepsy, five year remission status at the time of the reassessment questionnaire, type of epilepsy, and selected electro-clinical diagnoses. Age at onset of epilepsy was categorized as 0-2, 2-5, 5-10, and >10 years. Type of epilepsy was categorized according to the new ILAE Classification [13].

Developmental/Learning Disorders

All information about developmental/learning disorders was obtained by asking parents if their child had "...ever been diagnosed or described as being any of the following?" after which, we listed a series of developmental disorders, to which parents could respond by answering no, yes, maybe, or don't know. We dichotomized the results by combining responses of no, maybe, and don't know into one category. We considered children to be slow learners if their parents reported a concern regarding the diagnosis of mental retardation, developmental delay, slow learner, or learning disabled. We classified children as having a language disorder if they

were identified as having aphasic, language, or auditory processing disorders. Dyslexia was separately examined.

A hierarchical variable was created for developmental/learning disorders where children classified by their parents as having a language disorder in the first category. Excluding children in the first category, the second category consisted of slow learners. The referent group included children without either of these disorders.

Psychiatric Disorders

Parentally identified psychiatric disorders of interest included hyperactivity, attention deficit, obsessive compulsive, and conduct disorders. Additionally, cases and controls were compared with respect to depression, attempted suicide, and a history of self-injurious behavior other than attempted suicide.

Other Factors

Physical health conditions of interest included parentally identified diabetes, asthma, and migraine. Behavioral factors included trouble with the law and teen-age pregnancy.

Statistical Analysis

Frequencies and percentages were used to summarize categorical variables, and medians and interquartile ranges were used to describe continuous variables. Cases and controls were compared using McNemar's test for categorical variables and the Wilcoxon signed rank test for continuous variables. Conditional logistic regression was used to measure associations between risk factors of interest and epilepsy in crude analyses and in analyses stratifying by five year remission status, and age at onset. For the stratified analyses, age at onset was categorized as ≤ 2 years, 2-5 years, and ≥ 5 years. Variables that were found to be statistically significantly associated with epilepsy in the descriptive analyses were included in the conditional logistic regression analyses. We used SAS 9.1 (SAS Institute, Cary, NC, U.S.A.) for all statistical analyses.

Results

Demographics

Median age at onset (IQR) among the 217 cases was 5.8 (3.0 – 8.3) years. At the time of the questionnaire, 142 (65.4%) had been seizure-free for at least 5 years. The electro-clinical syndrome, benign epilepsy with central temporal spikes (BECTS), occurred in 27 (12.4%). In addition, type of epilepsy was genetic generalized for 60 (27.7%) cases, focal-unknown cause for 105 (48.4%) cases, and not classifiable for 25 (11.5%) cases. Median age at reassessment was 15.0 years for cases compared to 14.9 years among controls (IQR for cases=12.4 – 17.9 years; IQR for controls=12.2 – 19.3 years, $p=0.33$, Table 1).

Developmental/Learning Disorders

56 (25.8%) cases were identified as slow learners compared to 16 (7.4%) controls ($p<0.001$, Table 1). Parents reported that cases were slow learners more often than controls (OR=4.6, 95% CI=2.4 – 8.9, Table 2). Significantly increased odds were observed in all groups after stratification for five year remission status and age at onset (Table 2).

A language disorder was reported among 36 (16.6%) cases and 7 (3.2%) controls ($p<0.001$, Table 1). Cases had a 5.8-fold (95% CI=2.5 – 13.9) increased odds relative to controls of being described as having a language disorder. The results were similar after excluding the 27 cases diagnosed with BECTS (OR=6.4, 95% CI=2.5 - 16.4). Similar results were observed after

stratification by five year remission status, and in those with an age at onset ≥ 5 years (OR=10.0, 95% CI=2.3 – 42.8, Table 2). Cases and controls were similar with respect to dyslexia (1.8% in cases vs 0.9% in controls, $p=0.32$, Table 1).

In the hierarchical analysis, compared to children without developmental or learning disorders, parentally identified slow learners had a 3-fold increased odds (95% CI=1.5 – 5.9) of having epilepsy and parentally identified children with a language disorder had a 6.7-fold (95% CI=2.9 – 15.4) increased odds of having epilepsy. Although there was variation with respect to statistical significance across categories of age at onset, the associations remained after stratification by remission status (Table 2).

Psychiatric Disorders

Self-injurious behaviors other than suicide were reported in 5.1% of cases and 0.9% of controls (OR=5.5, CI=1.2-24.8, $p=0.013$). We found a marginally significant association for conduct disorder with 2.8% of cases and 0.5% of controls reported positive for this factor (OR=6.0, CI=0.7-49.8, $p=0.059$, Table 1). Cases and controls did not significantly differ with respect to depression (OR=1.2, 95% CI=0.5 – 2.5), attempted suicide (OR=3.0, 95% CI=0.6 – 14.9), hyperactivity (OR=1.9, 95% CI=0.7 – 4.7), attention deficit disorder (OR=1.7, 95% CI=0.9 – 3.3), and obsessive compulsive disorder (OR=2.5, 95% CI=0.5 – 12.9, Table 1).

Other Factors

Cases and controls were similar with respect to diabetes (0.5% in cases vs 1.4% in controls, $p=0.16$), asthma (13.4% in cases vs. 18.1% in controls, $p=0.15$), and migraine (8.8% in cases vs 7.4% in controls, $p=0.58$). An equal number of cases and controls had trouble with the law ($N=14$, 6.5% in each group). No case had a teen-age pregnancy compared to 1 (1.1%) control in the same age range.

Discussion

In young people with childhood-onset epilepsy of unknown or presumed genetic cause, parents reported a higher frequency of a variety of cognitive as well as behavioral and psychiatric disorders as compared to sibling controls. Many of these associations persisted after stratification by 5-year seizure remission status and age at onset.

Childhood-onset epilepsy of unknown or presumed genetic cause was significantly associated with parental report of being a slow learner. This association remained even after stratification by remission status and age at onset, although one might expect to see a stronger association with learning difficulties in cases with younger onset of epilepsy or whose epilepsy was not clearly resolved [14-16]. Others have reported substantial associations between young age at onset and overall decreases in cognitive function or mental retardation [14-16]. We did not see this carry through in a relatively cognitive normal group for a different but related outcome, learning disorder.

Parental report of a language or auditory processing disorder was also associated with epilepsy in our study. This finding is consistent with several studies demonstrating language deficits in children with epilepsy of unknown or presumed genetic cause [1,2,17].

A significantly higher proportion of children with epilepsy had attempted self-injurious behavior, other than suicide, compared to their siblings, consistent with previous research in this population [18], and with other work suggesting an association between childhood onset epilepsy and behavioral problems [19,20].

Our study has several strengths. First, we assessed behavioral and cognitive factors in children identified and followed prospectively since the initial diagnosis of epilepsy and who, as best could be ascertained had no underlying structural lesions or other metabolic insults to which their epilepsy could be attributed. Also, almost all of the cases had MRIs and were closely followed through direct contact and medical records, leaving little uncertainty in determining who had a structural metabolic condition [21]. Although children with such structural and metabolic insults are expected to experience much of the cognitive burden in epilepsy [4], our results show that cognitive and behavioral difficulties are also of concern in children free of these insults. Second, because a matched case-sibling-controlled study design was employed, we significantly reduced confounding, particularly by family factors, school district, access to educational diagnoses, medical care, sensitivity of physicians to diagnoses, and a host of other factors shared by siblings, while also gaining more efficiency. Third, as discussed previously by Berg and colleagues [18], the relatively low attrition in this study, less than 20%, yielded results that are more representative of the population from which our sample was drawn.

An important limitation of our study was that we had to rely on parental reporting to determine whether children had developmental, learning, or psychiatric disorders. Reporting bias would be a concern if parents perceived their children with epilepsy to be more impaired than their siblings without epilepsy. Although we had extensive medical records on cases, because we had not followed controls over time and had not requested access to their medical records over the same period of time that their siblings had been followed, we restricted case-control comparisons to information collected in the same standardized fashion. Another limitation is that the precision of our estimates was attenuated after stratification by remission status and age at onset for many variables. However the stratified analyses were not the primary analyses and therefore served to answer more exploratory questions.

Our findings indicate that childhood-onset epilepsy of unknown or presumed genetic cause among young people is associated with an increase in the occurrence of a variety of cognitive as well as behavioral and psychiatric difficulties. Future research should focus on the impact of these conditions on prognosis into adulthood.

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Table 1
Summary characteristics for cases and controls after nine-year reassessment

Variable	Cases (N=217)	Controls (N=217)	p-value ¹	OR (95% CI)
Factors				
Male	116 (53.5%)	95 (43.8%)	0.048	-
Median age, years	15.0 (12.4 - 17.9)	14.9 (12.2 - 19.3)	0.33	-
Age at onset, years				
0 - 2	36 (16.6%)	-	-	-
2 - 5	57 (26.3%)	-	-	-
5 - 10	89 (41.0%)	-	-	-
>10	35 (16.1%)	-	-	-
Five year remission	142 (65.4%)	-	-	-
Type of epilepsy				
Genetic generalized	60 (27.7%)	-	-	-
BECTS	27 (12.4%)	-	-	-
Focal-unknown cause	105 (48.4%)	-	-	-
Not classifiable	25 (11.5%)	-	-	-
Parent report of Developmental/Learning Disorders				
Mentally retarded, developmental delay, slow learner, or learning disabled	56 (25.8%)	16 (7.4%)	<0.001	4.6 (2.4 - 8.9)
Aphasic, language disorder, or auditory processing disorder	36 (16.6%)	7 (3.2%)	<0.001	5.8 (2.5 - 13.9)
Dyslexia	4 (1.8%)	2 (0.9%)	0.32	3.0 (0.3 - 28.8)
Parent report of Behavioral Disorders and Psychiatric Disorders				
Hyperactivity disorder	15 (6.9%)	9 (4.2%)	0.18	1.9 (0.7 - 4.7)
Attention deficit disorder	27 (12.4%)	17 (7.8%)	0.10	1.7 (0.9 - 3.3)
Obsessive compulsive disorder	5 (2.3%)	2 (0.9%)	0.26	2.5 (0.5 - 12.9)
Conduct disorder	6 (2.8%)	1 (0.5%)	0.059	6.0 (0.7 - 49.8)

Variable	Cases (N=217)	Controls (N=217)	p-value ¹	OR (95% CI)
Depression	17 (7.8%)	15 (6.9%)	0.69	1.2 (0.5 – 2.5)
Attempted suicide ²	6 (2.8%)	2 (0.9%)	0.16	3.0 (0.6 – 14.9)
Other self-injurious behavior ²	11 (5.1%)	2 (0.9%)	0.013	5.5 (1.2 – 24.8)
Other				
Diabetes	1 (0.5%)	3 (1.4%)	0.16	-
Asthma ³	29 (13.4%)	39 (18.1%)	0.15	0.7 (0.4 – 1.2)
Migraines	19 (8.8%)	16 (7.4%)	0.58	1.2 (0.6 – 2.6)
Teen-age pregnancy ^{2,4}	0 (0.0%)	1 (1.1%)	-	-
Trouble with law ³	14 (6.5%)	14 (6.5%)	1.00	1.0 (0.4 – 2.3)

Data are frequency (%) or median (interquartile range).

¹ P-values reflect the results of the McNemar's Test for categorical variables and Wilcoxon Signed Rank Test for continuous variables.

² Missing information for 2 (0.9%) controls.

³ Missing information for 1 (0.5%) control.

⁴ Only those between 13 and 19 years of age are included in this analysis.

Table 2

Results of conditional logistic regression analysis for total sample and stratified by remission status and age at onset

Variable	Overall OR (95% CI)	Remission OR (95% CI)	Non-Remission OR (95% CI)	Onset Age ≤ 2 years OR (95% CI)	Onset Age 2 - 5 years OR (95% CI)	Onset Age ≥ 5 years OR (95% CI)
Slow Learner, (Mentally retarded, developmental delay, slow learner, or learning disabled)						
No	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Yes	4.6 (2.4 - 8.9)	4.1 (1.8 - 9.5)	5.5 (1.9 - 16.0)	3.7 (1.02 - 13.1)	11.0 (2.6 - 46.8)	3.0 (1.2 - 7.6)
Auditory processing disorder (Aphasic, language disorder, or auditory processing disorder)						
No	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Yes	5.8 (2.5 - 13.9)	3.6 (1.3 - 9.7)	17.0 (2.3 - 127.7)	4.0 (0.8 - 18.8)	3.5 (0.7 - 16.8)	10.0 (2.3 - 42.8)
Multiple developmental and auditory comparison						
None	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Slow Learner	3.0 (1.5 - 5.9)	2.9 (1.2 - 7.3)	3.2 (1.2 - 9.2)	2.7 (0.5 - 15.6)	12.2 (2.7 - 56.3)	1.2 (0.5 - 3.1)
Language Disorder	6.7 (2.9 - 15.4)	4.4 (1.6 - 12.1)	13.5 (3.0 - 60.9)	(0.97 - 16.2)	5.4 (1.1 - 27.2)	11.9 (2.7 - 52.3)