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Psychiatric and neurodevelopmental disorders in childhood-onset epilepsy

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Abstract

Childhood-onset epilepsy is associated with psychiatric and cognitive difficulties and with poor social outcomes in adulthood. In a prospective cohort of young people with epilepsy, we studied psychiatric and neurodevelopmental disorders (PD and ND) and epilepsy-related characteristics, all factors which may influence long-term social outcomes. 501 subjects, 159 with complicated (IQ<80 or brain lesion) and 342 with uncomplicated epilepsy were included. PD and ND were more common in complicated epilepsy ($p<0.005$). In uncomplicated epilepsy, externalizing but not internalizing disorders were strongly associated with ND. Internalizing disorders and ND were associated with lack of 5-year remission. Type of epilepsy was not associated with NDs or PDs. Various comorbid conditions in epilepsy cluster together and are modestly associated with imperfect seizure control. These need to be considered together in evaluating and managing young people with epilepsy and may help explain long-term social outcomes above and beyond poor seizure control.

Keywords

Co-morbidity; neurodevelopmental disorders; psychiatric disorders; epilepsy; childhood

Introduction

There is an extensive literature documenting the increased occurrence of psychiatric and neurodevelopmental disorders in association with epilepsy [1]. A substantial portion of the association between epilepsy and neurodevelomental disorders is likely a reflection of intellectual disability and occurs in association with underlying structural brain lesions and other neurological disorders frequently seen in people with epilepsy [2,3]. In elderly adults, the association between epilepsy and most disorders such as depression may also be driven by underlying brain lesions [4].

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Even in people with epilepsy whose cognition is within the normal range and who have no underlying structural brain abnormalities ("uncomplicated epilepsy"), there is evidence of increased occurrence of psychiatric disorders and subtle cognitive or developmental problems [5–10]. Some studies find that children with lower levels of cognitive function but who are still within the normal range [9,11,12] or only mildly impaired range are also the ones most likely to have psychiatric disorders [13]. The relationship among these factors and with epilepsy-related factors has not been thoroughly examined although evidence from long-term studies suggests that social outcomes are worse than expected in people with "uncomplicated" epilepsy [14–16].

We studied the prevalence of reported psychiatric disorders and neurodevelopmental spectrum disorders in a community-based cohort study of young people with childhood-onset epilepsy. We examined the association of psychiatric and neurodevelopmental disorders with each other. We also examined the association between these disorders and various features of epilepsy to determine which characteristics in young people with epilepsy identified individuals with a greater or lesser prevalence of neurodevelopmental and psychiatric disorders.

1) Methods

Analyses were conducted in the Connecticut study of epilepsy cohort. The study initially recruited children from the offices of 16 of the 17 pediatric neurologists practicing in Connecticut during the period 1993–1997. We also contacted and attempted to recruit patients from pediatricians and adult neurologists in the state; however, given the high concentration of pediatric neurologists in Connecticut, pediatricians almost always referred to one of these specialists [17]. The cohort has been closely followed since then with phone calls every 3–4 months, review of medical records on an ongoing basis, and additional questionnaires administered at 5 and at 8–9 years after initial diagnosis of epilepsy. Underlying causes of epilepsy were carefully characterized based upon all information in the medical records as well as neuroimaging evaluations done for research purposes. The type of epilepsy was characterized at initial diagnosis and updated over time as additional information became available. Remission status was determined as of the date on which the 9-year interview was completed. Interviews at 8–9 years were usually done with a parent or guardian.

We assessed the reported cumulative history of ever having had several specific psychiatric diagnoses and neurodevelopmental spectrum disorders from diagnosis to 9 years later based upon questions in the 9-year interview as well as review of the accumulated medical records. An endorsement with "yes" on the questionnaire or report of documentation of the diagnosis in the medical record with or without specific treatment was considered as evidence that the individual had the disorder. When the interview was negative but the medical record provided clear evidence that a diagnosis had been made, the medical record was used. Psychiatric disorders included internalizing disorders (depression, anxiety, obsessive compulsive disorder (OCD), bipolar disorder, and schizophrenia) and externalizing disorders (attention deficit/hyperactivity disorder (ADHD), conduct disorder (CD) and oppositional defiant disorder (ODD)).

For neurodevelopmental spectrum disorders, we asked whether the subject had been diagnosed with a developmental delay, learning disorder, mental retardation, autism spectrum disorder, auditory processing disorder, and dyslexia.

Neurocognitive testing was performed for research purposes in 335 members of the cohort. An additional 44 subjects had neurocognitive test results performed for clinical purposes,

and those results were available. For the remaining subjects, determinations were made based on clinical information including obvious severe intellectual disability, performance in school (e.g. taking advanced placement course), and assessments made by the treating neurologist and others involved in the patient's care. For these analyses, level of cognitive function was defined as within the normal range, consistent with a full scale IQ (FSIQ) ≥80 or low/impaired (consistent with FSIQ<80) based on assessments and evaluations described previously [18].

"Uncomplicated" epilepsy was defined as epilepsy in an individual with estimated FSIQ of ≥80 and who had no evidence of a underlying structural brain lesion to which the epilepsy could be attributed [19]. Epilepsy was considered "complicated" in subjects with FSIQ<80 or evidence of a structural lesion. This is comparable to the use of these terms by others [2]. A history of ever having received special education or related services was also ascertained as part of the interview. This is a marker of difficulties in the school setting and would be anticipated to be strongly associated with low IQ as well as the presence of neurodevelopmental spectrum disorders. We used this as an additional check for the reporting of neurodevelopmental spectrum disorders.

Bivariate analyses were conducted using chi-square tests and t-tests as appropriate for the data. Associations are represented as prevalence ratios. Multiple logistic regression was used to perform multivariable analyses with a binomial response function for modeling prevalence [20].

At the outset, parents provided written informed consent and study subjects gave written or verbal ascent as appropriate for age to participate in the original study. As study subjects attained the age of majority, they were recruited to participate as adults unless intellectual disability precluded their ability to do so. In such cases, their parents continued to provide permission. All procedures have been approved by the Institutional Review Boards of the participating institutions and were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

3) Results

The original cohort consisted of 613 children of whom 501 (81.7%) participated in the 9-year interview and had completed, usable interviews. Of those who were not included, 28 were actively followed but declined to participate in the interview, 70 had already been lost prior to this phase of the study, 13 had died prior to the time of the interview, and one interview had to be excluded.

In the interviewed group, 247 (49.3%) were female. The average ages at onset of epilepsy and at time of participating in the interview were 5.8 years (SD=4.0) and 15.3 years (SD=4.2). The interviews were targeted to be done approximately 9 years after initial diagnosis of epilepsy. The mean interval was 9.5 years (SD=1.4, range 6.6 to 15.1). The epilepsy was classified as uncomplicated in 342 (68.3%) of the included cohort.

One or more psychiatric disorders was reported in 152 (30.3%) including 80 with internalizing disorders (depression (N=67), anxiety (N=25), OCD (N=14), bipolar disorder (N=6) or schizophrenia (N=2)) and 111 with externalizing disorders (ADHD (N=104), CD (N=22), or ODD (N=5)). Multiple psychiatric disorders were reported in 57 (11.4%) study subjects including 39 who had both externalizing and internalizing disorders. One or more neurodevelopmental spectrum disorders was reported in 209 (41.7%) including developmental delay (N=160), language problem (N=112), dyslexia (N=14), learning disorder (N=135), and autistic spectrum disorder (ASD, N=26). Multiple neurodevelopmental spectrum disorders were reported in 145 (28.9%).

Special education or related services had been received by 296 (59.1%) of the interviewed cohort, including 144 (90.6%) in the complicated group and 152 (44.4%) in the uncomplicated group ($p<0.0001$). Of subjects with reported neurodevelopmental spectrum disorders, 100% in the complicated group and 75/79 (95%) in the uncomplicated group had received special services.

Comparison of complicated and uncomplicated epilepsy

Both neurodevelopmental and psychiatric disorders were more common in children with complicated than with uncomplicated epilepsy (Table 1). The associations with psychiatric disorders were almost entirely due to externalizing disorders which occurred in 62 (18.1%) of the uncomplicated and 49 (30.8%) of the complicated group ($p=0.002$).

Association between neurodevelopment and psychiatric disorders (Table 2)

Overall, 115/349 (33.0%) with no psychiatric disorders had neurodevelopmental disorders versus 94/152 (61.8%) of those with any psychiatric disorders ($p<0.0001$). This relationship was stronger for externalizing than for internalizing disorders. Within the complicated epilepsy group, however, there was no association between neurodevelopmental disorders and psychiatric disorders overall or separately for internalizing or externalizing disorders. By contrast, for the uncomplicated group, psychiatric disorders and neurodevelopmental disorders were strongly associated ($p<0.0001$). This was observed for both internalizing and for externalizing disorders but was stronger for externalizing.

Overall and separately within complicated and uncomplicated epilepsy groups, internalizing and externalizing disorders were strongly associated with each other. In the full group, 35% with versus 11% without externalizing disorders also had internalizing disorders ($p<0.0001$). Within the complicated group, the corresponding figures were 31% versus 11% ($p=0.002$), and within the uncomplicated group, the figures were 39% versus 10% ($p<0.0001$).

Within the complicated group, 9/22 (41%) with depression had anxiety versus 4/137 (3%) of those without depression ($p<0.0001$). In the uncomplicated group, the comparable figures were 6/45 (13%) and 6/297 (2%) ($p=0.002$). ADHD co-occurred with depression or anxiety. Within the complicated group, 12/46 (26%) of those with ADHD had depression or anxiety versus 14/113 (12%) of those without ADHD ($p=0.03$). The corresponding percentages in the uncomplicated group were 21/58 (36%) and 30/284 (11%) ($p<0.0001$).

Uncomplicated epilepsy

Because some of the subgroups were too small for more detailed analysis within the complicated group, further analyses focused primarily on the uncomplicated group (N=342; table 3). Within this group, we found some fairly large differences in the factors associated with having internalizing versus externalizing disorders. In particular, older age, both at onset and at interview, were strongly correlated with internalizing but not with externalizing disorders or neurodevelopmental spectrum disorders. Although a history of having failed trials of at least two AEDs (pharmacoresistance) was not associated with greater proportions having psychiatric or neurodevelopmental spectrum disorders in this uncomplicated epilepsy group, not being in five-year remission at the time of the interview and, to a lesser extent, never having been five-years seizure-free, were significantly associated with a greater proportion reporting both internalizing and neurodevelopmental disorders but not externalizing disorders. Of the additional variables we considered, only male sex was strongly associated with externalizing disorders but not with neurodevelopmental disorders.

To summarize these complex inter-relationships, we performed a series of logistic regression analyses to identify independent factors correlated with internalizing,

externalizing, and neurodevelopmental spectrum disorders (table 4). We selected age at interview rather than age at onset for these models as this made sense in light of what is known of the epidemiology of these disorders in general.

The main factors correlated with internalizing disorders were externalizing disorders ($p<0.0001$) and older age at interview ($p=0.0003$). After adjustment for these two factors, 5-year remission status at the time of interview was associated with a 43% lower prevalence of internalizing disorder ($p=0.04$), 96% of which was depression and/or anxiety. The main factors associated with externalizing disorders were internalizing disorders ($p<0.0001$), neurodevelopmental spectrum disorders ($p<0.0001$), and male gender ($p<0.0001$). Finally, neurodevelopmental spectrum disorders were associated with externalizing disorders ($p<0.0001$) and 5-year remission status at the time of the interview ($p=0.0007$).

Discussion

Psychiatric and neurodevelopmental disorders are more common in young people with epilepsy than in the general population [2]. Our analyses identified factors within a group of young people with epilepsy that were associated with a higher prevalence of these disorders.

Complicated epilepsy

Higher levels of externalizing disorders, were found in young people with complicated epilepsy (low IQ or known structural brain lesion) than in those with uncomplicated epilepsy. Neurodevelopmental spectrum disorders were reported in 80% of the complicated group. In this group, neurodevelopmental disorders were not associated with an increased prevalence of psychiatric disorders overall or specifically for internalizing or externalizing disorders. In interpreting this particular lack of association, one should consider that the definition of complicated epilepsy was largely determined by low IQ which itself is often an important determinant or simply a reflection of many neurodevelopmental spectrum disorders. These, in turn, are strongly correlated with externalizing disorders. Thus there is considerable overlap in definitions of “complicated” and neurodevelopmental disorder. Internalizing disorder (e.g. depression and anxiety), on the other hand, may be more difficult to detect in people with intellectual disability for at least three reasons: First, internalizing diagnoses generally do not involve outward manifestations and may consequently be less apparent, particularly in mild to moderate cases. Second, and related to that, individuals with low IQ might not have the verbal skills needed to report or describe their emotions and feelings. Third, the diagnosis of internalizing disorders in individuals with moderate to severe intellectual disability requires clinicians with specialized expertise in diagnosing psychiatric disorders in individuals with cognitive compromise or scales specially developed and validated in intellectually disabled individuals [21]. In general, this is an underserved segment of the population when it comes to mental health needs.

Uncomplicated epilepsy

Although low IQ or the designation of developmental “disability” (a term used in some studies) identifies the most extreme end of a spectrum of cognitive disorders, less severe forms of these disorders may be present in people with normal neurological exams, normal neuroimaging, and normal overall intelligence as determined by an IQ score, what we termed “uncomplicated epilepsy.” Nearly a quarter of the “uncomplicated” epilepsy group also reported having neurodevelopmental spectrum disorders. This is more than the prevalence in matched sibling controls from the same study [22].

In the uncomplicated group, neurodevelopmental and externalizing disorders were strongly associated with each other. This result likely reflects what others have found; externalizing

disorders, such as ADHD, are associated with developmental abnormalities [23] and brain dysfunction [24] involving deficits in attention, executive function, and self-regulation which present clinically as a learning disorder [25]. By contrast, after adjustment for externalizing disorders, there was no independent association between the neurodevelopmental disorders and internalizing disorders such as depression. While depression is strongly associated with epilepsy, it is perhaps for other reasons [26].

Analysis of epilepsy-related factors yielded expected associations, particularly for current age and internalizing disorders and for male gender with externalizing disorders. Of particular interest was the lack of any compelling differences across different types of epilepsy. There is a large literature that examines psychiatric and learning problems in young people with epilepsy usually by comparing those with a specific form of epilepsy to non-epilepsy controls. Our direct comparison of different forms of epilepsy to each other did not yield strong evidence that specific subtypes of epilepsy were differentially associated with psychiatric or neurodevelopmental disorders. This suggests a general impact for epilepsy, one that does not appear to be specific to particular forms of epilepsy.

Although pharmacoresistance (failure of two AEDs to control seizures) was not associated with psychiatric disorders, not achieving five-year remission, particularly at the time of the interview, was modestly correlated with neurodevelopmental disorders and internalizing disorders (primarily depression or anxiety). It is unclear why people with internalizing disorders would be less likely to be in remission than those without. Prior work has shown that depression is associated with an increased risk of developing epilepsy and particularly uncomplicated epilepsy [27]. Depression and anxiety have been associated with an increased risk for further seizures in people with newly treated epilepsy [28] and for pharmacoresistance [29]. In a prevalent sample of children with treated epilepsy, a marker of seizure severity was also correlated with depression and emotional problems [30]. Finally, Kanner et al. reported that lifetime psychiatric history, primarily mood disorders, predicted a worse prognosis for remission after anterior temporal lobectomy [31]. Taken together, these findings suggest a fundamental relationship of the occurrence and control of seizures with psychiatric disorders. Our findings in uncomplicated childhood onset epilepsy are consistent with these other published observations. These studies have, however, considered many different forms of epilepsy at different ages and of different causes as well as considered different types of seizure outcomes from onset of epilepsy to response to resective surgery. Whether there is a single mechanism unifying these diverse findings or not remains to be seen.

Older cohort studies have reported relatively poor long-term social outcomes in terms of finishing school, getting married, and employment in individuals with childhood onset epilepsy. Some have highlighted that, overall, it is people with borderline or clearly abnormal intellectual function who are at greatest risk of the worst social outcomes [32,33]. Others have focused on adults of normal intelligence with childhood-onset epilepsy who roughly fit our definition of uncomplicated epilepsy. The results are mixed in that some studies find lack of remission associated with poor social outcomes whereas others do not. [14,16,34]. How, if at all, psychiatric disorders play a role in these long-term associations requires further investigation.

Our data clearly demonstrate the expected strong association between use of special education resources, an indication of problems in school, and externalizing as well as neurodevelopmental disorders. A separate cross-sectional study of treated prevalent epilepsy found similar associations with special education needs being seen much more frequently in children with hyperactivity/inattention and conduct problems than in children without [30]. The psychiatric and neurodevelopmental disorders that we have studied are present during

the time most of the young people were in school, including college, or entering the work force. They are of the nature to cause difficulties with school and job performance. School difficulties are not the same as long-term social outcomes which we have not yet been able to study. They may, however, be markers for disturbances that can have longer-term implications. Potentially the long-term impact of having had epilepsy on various markers of social success in adulthood is related to neurodevelopmental and psychiatric disorders earlier in life, whether or not they persist into adulthood.

Associations between internalizing and externalizing disorders such as we found in both complicated and uncomplicated epilepsy are also found in the general population [35]. In examining the co-occurrence of internalizing and externalizing disorders, the most common association is that between ADHD and depression or anxiety with a 6 to 8-fold increased occurrence of ADHD in the presence of anxiety or of depression [36]. These disorders co-occurred in both complicated and uncomplicated epilepsy with a comparable relationship observed for uncomplicated epilepsy. Within internalizing disorders, current depression is associated with a 28-fold increase in current anxiety [36]. While these disorders were comorbid in both complicated and uncomplicated epilepsy, the magnitude of the association (as measured by a prevalence ratio) was somewhat less than that observed in the general population.

As with any study, there are numerous weaknesses as well as strengths. We did not have diagnostic interviews for determining psychiatric and neurodevelopmental diagnoses. On the other hand, we did have extensive information from the neurological records maintained over many years which allowed confirmation and occasionally augmentation of parent reports. Of note, there are several large scale surveys reported in the literature that identify similar diagnoses based simply on a questionnaire with no reference to medical records or standardized assessments (e.g. [37]). The fact that nearly everyone with reported neurodevelopmental spectrum disorders received some special education services suggests that the reporting of these disorders did bear a relationship to true difficulties experienced by the children. We also note that the parents and children in the cohort had been involved in the study for many years before participating in this interview and were familiar with the study staff who administered the interview. This likely made frankness in reporting of the disorders being queried easier as parents had already shared this and related information with the interviewers over the years.

In doing this kind of research, there will always be some tension between precision in diagnoses and representativeness of the study group. In this case, the Connecticut study is representative of individuals with newly diagnosed epilepsy in a defined geographic region. As previously reviewed, key benchmark features of this cohort (age at onset, proportions with intellectual disability, absence epilepsies, and refractory epilepsy) were similar to those in an independent population-based study [3]. Information about underlying cause, types of epilepsy, and seizure outcomes has been rigorously collected prospectively. Participation in the 9-year interview was excellent both for the original cohort of 613 (81.7%) and for those still in active follow-up (94.5%). Over 90% of the cohort had neuroimaging, 85% with MRI [3]. Consequently, clinically relevant, gross structural abnormalities would have been identified, and we can be reasonably confident not to have missed individuals whose difficulties might be better attributed to underlying structural lesions. In addition, over half of the respondents had cognitive testing done by the research study while the others had assessments and other sources of information that allowed for reasonable estimation of cognitive function [18]. Although AEDs may sometimes impact cognitive test performance, a previous investigation in this cohort did not suggest that this was causing any significant effect, at least at the time that research testing was performed [38].

Our findings have some important implications. Given the strong association between internalizing and externalizing disorders in uncomplicated epilepsy, it suggests that clinicians and educators should evaluate young people with epilepsy for internalizing disorders if they are known to have externalizing disorders. These results may also have important practical implications for management and counseling of children with epilepsy, perhaps even after their epilepsy resolves, as they may be at risk for the later occurrence of internalizing disorders. In terms of future research studies of psychiatric disorders in people with epilepsy, it would seem important to incorporate an assessment of cognitive function, neuro-imaging and of neurodevelopmental spectrum disorders. This is true for studies examining psychiatric disorders within groups of epilepsy patients but also for comparing people with epilepsy to controls without.

Clearly, there are additional questions that cannot yet be fully addressed in this cohort regarding the impact of earlier life disorders on long-term social outcomes in adulthood. It is still unclear from the literature whether young people whose epilepsy is in complete remission, are still at risk for impaired social outcomes in adulthood. The potential role for psychiatric and neurodevelopmental disorders, whether persistent or not, to have an impact on long-term social success in conjunction with or independent of seizure remission is one that has not been fully explored. If the early disorders have a persistent effect regardless of seizure remission, this could represent a hidden burden of epilepsy that is relatively unappreciated, especially in people whose seizures, the most dramatic manifestation of epilepsy, have resolved and are no longer treated.

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Table 1

Psychiatric and neurodevelopmental spectrum disorders in complicated versus uncomplicated epilepsy.

	Complicated * (N=159)	Uncomplicated** (N=342)	p-value
Any psychiatric disorder			
None	98 (61.6%)	251 (73.4%)	0.008
Present	61 (38.4%)	91 (26.6%)	
Internalizing disorder			
None	132 (83.0%)	289 (84.5%)	
Present	27 (17.0%)	53 (15.5%)	0.67
Externalizing disorder			
None	110 (69.2%)	280 (81.9%)	
Present	49 (30.8%)	62 (18.1%)	0.002
Neurodevelopmental disorder			
None	29 (18.2%)	263 (76.9%)	<0.0001
Present	130 (81.8%)	79 (23.1%)	

* Complicated: Subject has cognitive function level consistent with IQ<80 or there is a documented brain lesion or related condition to which the occurrence of epilepsy has been attributed

** Uncomplicated: Subject has cognitive function consistent with IQ>80 and no identified structural brain lesion or similar condition to which the epilepsy can be attributed.

Table 2

Associations between psychiatric disorders and neurodevelopmental spectrum disorders.

Total sample (N=501)				
	N	**NSD* – no**	**NSD - yes**	**p-value**
PD* – no	349	234 (67.0)	115 (33.0)	
PD - yes	152	58 (38.2)	94 (61.8%)	<0.0001
Internalizing –no	421	253 (60.1)	168 (39.9)	
Internalizing – yes	80	39 (48.7)	41 (51.3)	0.06
Externalizing- no	390	257 (65.9)	133 (34.1)	<0.0001
Externalizing - yes	111	35 (31.5)	76 (68.5)	
Complicated epilepsy only (N=159)				
	N	**NSD – no**	**NSD - yes**	p-value
PD – no	98	20 (20.4)	78 (79.6)	
PD - yes	61	9 (14.8)	52 (85.3)	0.37
Internalizing –no	132	23 (17.4)	109 (82.6)	
Internalizing – yes	27	6 (22.2)	21 (77.8)	0.56
Externalizing- no	110	23 (20.9)	87 (79.1)	
Externalizing - yes	49	6 (12.2)	43 (87.8)	0.19
Uncomplicated epilepsy only (N=342)				
	N	**NSD – no**	**NSD - yes**	p-value
PD – no	251	214 (85.3)	37 (14.7)	
PD - yes	91	49 (53.9)	42 (46.2)	<0.0001
Internalizing –no	289	230 (79.6)	59 (20.4)	
Internalizing – yes	53	33 (62.3)	20 (37.7)	0.006
Externalizing- no	280	234 (83.6)	46 (16.4)	
Externalizing - yes	62	29 (46.8)	33 (53.2)	<0.0001

NSD, Neurodevelopmental spectrum disorder; PD, psychiatric disorder

Table 3

Association between clinical factors and psychiatric and neurodevelopmental disorders in the portion of the cohort with uncomplicated epilepsy.

	N	Any Psychiatric Diagnosis	Internalizing Disorders	Externalizing Disorders	Neurodevelopmental Spectrum Disorders
Sex					
Female	171	41(24.0)	31(18.1)	19(11.1)	36(21.1)
Male	171	50(29.2)	22(12.9)	43(25.2)	43(25.2)
p-value		0.27	0.18	0.0008	0.37
Onset Age					
<2 Years	52	6(11.5)	1(1.9)	6(11.5)	11(21.2)
2–5 Years	84	20(23.8)	7(8.3)	16(19.1)	21(25.0)
5–10 Years	145	43(29.7)	29(20.0)	25(17.2)	34(23.5)
10+ Years	61	22(36.1)	16(26.2)	15(24.6)	13(21.3)
p-value*		0.002	<0.0001	0.14	0.94
Interview Age					
<10 Years	28	1(3.6)	1(3.6)	1(3.6)	5(17.9)
10–15 Years	123	24(19.5)	8(6.5)	21(17.1)	28(22.8)
15–20 Years	134	43(32.1)	26(19.4)	27(20.2)	32(23.9)
20+ Years	57	23(40.4)	18(31.6)	13(22.8)	14(24.6)
p-value*		<0.0001	<.0001	0.05	0.53
Syndrome					
BECTS+	57	17(29.8)	12(21.1)	11(19.3)	8(14.0)
CAE	51	12(23.5)	4(7.8)	10(19.6)	13(25.5)
JAE/ JME	27	10(37.0)	7(25.9)	6(22.2)	7(25.9)
Other	207	52(25.1)	30(14.5)	35(16.9)	51(24.6)
p-value*		0.51	0.11	0.89	0.36
Failed at least two drugs					
No	302	78(25.8)	43(14.2)	54(17.9)	68(22.5)
Yes	40	13(32.5)	10(25.0)	8(20.0)	11(27.5)
p-value		0.37	0.08	0.74	0.48

	N	Any Psychiatric Diagnosis	Internalizing Disorders	Externalizing Disorders	Neurodevelopmental Spectrum Disorders
5+ years seizure-free at time of interview					
No	93	32(34.4)	22(23.7)	22(20.6)	37(34.6)
Yes	249	59(23.7)	31(12.5)	40(17.0)	42(17.9)
p-value		0.05	0.001	0.43	0.0007
Ever seizure-free >5 years					
No	93	32(34.4)	22(23.7)	20(21.3)	30(31.9)
Yes	249	59(23.7)	31(12.5)	42(16.9)	49(19.8)
p-value		0.05	0.001	0.35	0.02

[+]BECTS, Benign Epilepsy with Centro-Temporal Spikes; CAE, Childhood Absence Epilepsy, JAE, Juvenile Onset Epilepsy; JME, Juvenile Myoclonic Epilepsy

[*]P-value for trend

Table 4

Results of logistic regression analyses to identify the factors that had independent associations with neurodevelopmental, internalizing, and externalizing disorders.

	Prevalence Ratio for each kind of disorder*	95% CI	p-value
Neurodevelopmental spectrum disorders			
Externalizing disorders	3.13	2.00, 4.90	<0.0001
5-year remission at the time of interview	0.55	0.35, 0.85	0.007
Internalizing disorders			
Externalizing disorders	3.24	1.88, 5.58	<0.0001
Age at interview*	1.89	1.34, 2.68	0.0003
5-year remission at the time of interview	0.57	0.34, 0.97	0.04
Externalizing Disorders			
Internalizing disorders	2.99	1.77, 5.07	<0.0001
Neurodevelopmental Disorders	3.03	1.82, 5.05	<0.0001
Male sex	2.34	1.36, 4.03	<0.0001

* per each increment in age group