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FULL-LENGTH ORIGINAL RESEARCH

Cognitive outcomes in children who present with a first unprovoked seizure

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Summary

Purpose: To determine the long-term cognitive and educational outcomes in children prospectively identified at the time of a first unprovoked seizure.

Methods: A cohort of children with a first unprovoked seizure was enrolled and followed for a mean of 15 years. Cognitive function and educational outcomes were determined 10 or more years after the first seizure via standardized neuropsychological tests, school records, and structured interviews. Children with symptomatic etiology were excluded from the analysis. When available, siblings of study subjects were recruited as normal controls. Primary educational outcome was defined as enrollment into special education services or grade repetition.

Results: Twenty-eight percent of (43 of 153) of children with a single seizure and 40% (42 of 105) of children with epilepsy received special education service or repeated a grade ($p = 0.05$). There was a statistically significant trend in which the children with more seizures tended to require special education or repeat a grade more often (28% in single seizure group vs. 34% in 2–9 seizure group vs. 64% in ≥10 seizure group; $p = 0.004$). Of 163 subjects who completed neuropsychological testing, children with single seizures tended to score higher than children with epilepsy on Wide Range Achievement Test-3 (WRAT) reading ($p = 0.08$), Test of Non-Verbal Intelligence-II (TONI-II) ($p = 0.02$), and Wechsler Intelligence Scale for Children (WISC)/Wechsler Adult Intelligence Scale (WAIS) ($p = 0.07$). There was no statistically significant difference between children with a single seizure and sibling controls.

Conclusion: The results suggest that children with a single seizure represent a group that is distinctly different from children with epilepsy and are more similar to sibling controls. In contrast, even children with very mild epilepsy have significantly worse educational outcomes.

KEY WORDS: Cognition, Education, Neuropsychology, Children, Epilepsy, Seizure.

Childhood seizures are common, with an estimated rate of unprovoked seizure in 2% and epilepsy in 1% of all children by age 16 (Hauser & Kurland, 1975; Hauser et al., 1993; Berg, 1995). Although the prognosis for remission of seizures is generally favorable, published data indicate a long-term adverse impact of childhood epilepsy on education, employment, and marriage (Brorson & Wranne, 1987; Mitchell et al., 1991; Camfield et al., 1993; Jalava & Sillanpaa, 1997; Jalava et al., 1997; Kokkonen et al., 1997; Sillanpaa et al., 1998). The reasons for the poor educational outcomes are not entirely clear; however, the association between epilepsy and cognitive comorbidity has been well described (Espie et al., 1997; Engelberts et al., 2002; Berg et al., 2004; Elger et al., 2004; Besag, 2006; Hermann et al., 2007, 2008). Cognitive comorbidities can be present in children with newly diagnosed epilepsy, well-controlled epilepsy requiring antiepileptic drugs (AEDs), as well as in children who are in remission and no longer require AEDs (Wirrell et al., 1997; Austin et al., 2002; Berg et al., 2005). It is not clear whether those comorbidities are secondary to the frequency of seizures, their treatment with AEDs, social stigma, or a comorbid neurologic disorder, as these factors are strongly interrelated (Northcott et al., 2005; Hessen et al., 2006; Berg et al., 2007). It is less well documented in the literature whether children with a single unprovoked seizure have the same scope of issues described in children with epilepsy. A better understanding of the long-term cognitive and educational outcomes of childhood-onset seizures is important for designing early interventions to improve long-term outcomes in children at risk. We report the results of the cognitive and educational outcomes of children with a first unprovoked seizure, obtained in a prospective study with more than 10 years of follow-up.

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Methods

Cohort description

In the original prospective cohort study, 407 children and adolescents with a first unprovoked seizure were recruited

and followed for a median of 15 years. These were identified at Montefiore Medical Center, Jacobi Medical Center, North Central Bronx Hospital, as well as the private practices of the authors between October 1983 and August 1992. Eligibility criteria included children ranging from 1 month to 19 years of age, and presentation with a first unprovoked afebrile seizure. At the time of the initial visit, informed consent was obtained from the parent, as well as informed assent from the child whenever appropriate. For the purpose of this study, a child with a single seizure was classified by characteristic electroencephalography (EEG) features, imaging study, history, and physical examination. Details of the inclusion and exclusion criteria for this cohort as well as of the initial evaluation have been previously reported (Shinnar et al., 1990, 1996, 1999, 2000, 2001). The cohort consisted of 75 children with idiopathic etiology (neurologically normal children with presumed genetic epilepsies based on age of onset, seizure semiology, and the characteristic EEG findings (Commission on Classification and Terminology 1989; Commission on Epidemiology and Prognosis, 1993), 253 children with cryptogenic etiology (all cases not remote symptomatic or idiopathic), and 79 children with remote symptomatic etiology (children with static encephalopathy from birth and/or those that sustained a prior neurologic insult, such as a stroke or significant head trauma). This study was conducted prior to the new proposed International League Against Epilepsy (ILAE) Classification scheme (Berg et al., 2010) and, therefore, is based on the classification accepted at the time the study was conducted (Commission on Classification and Terminology, 1981, 1989; Commission on Epidemiology and Prognosis, 1993).

For this analysis, children with remote symptomatic etiology were excluded, as these children were known to be neurologically abnormal prior to the onset of seizure, and, therefore, expected to have worse cognitive and epilepsy outcomes. Of 407 subjects and 101 siblings from the original cohort, 328 subjects and 82 sibling controls met the inclusion criteria. The final cohort for this analysis consisted of 258 subjects and 78 sibling controls whose educational outcomes were obtained 10 or more years after initial entrance into the study. The study was approved by the Institutional Review Board of Montefiore Medical Center and the Albert Einstein College of Medicine. Informed consent and assent when applicable were obtained for all subjects.

Data collection

Details including seizure characteristics, duration, and number of seizures in 24 h, and any treatment given were collected. Additional information regarding prior provoked seizures, prior neurologic insults, birth history, and family history was also collected. Physical and neurologic examinations were performed on all children. EEG studies were scheduled for all cases. Neuroimaging studies [computed tomography (CT) or MRI] were performed whenever clinically indicated. All cases had an MRI of the brain as part of the reevaluation between 5 and 10 years after initial evaluation. Upon enrollment, subjects were followed by telephone interviews every 3 months for ascertainment of any seizure recurrence. In those children with recurrence, records of any emergency medical care were reviewed, and the children were reevaluated. Recurrence was defined as an unprovoked seizure occurring more than 24 h after the first seizure. Etiology and epilepsy syndrome were classified in all children at the time of initial evaluation and reclassified at the end of study in 2003 in accordance with International League Against Epilepsy (ILAE) criteria (Commission on Classification and Terminology, 1981, 1989; Commission on Epidemiology and Prognosis, 1993). Etiology and epilepsy syndrome classification were stable in most of subjects (84%) over time, with a change in either localization only (n = 13), etiology only (n = 20), both localization and etiology (n = 22), or epilepsy syndrome within the same category of localization and etiology (n = 9). The classification from 2003 was used for this analysis, as it was the most accurate with all the available information including MRI results.

Neuropsychological testing

After 10 or more years following the first seizure, a structured interview was administered to all subjects in the cohort to assess educational history. To get a uniform measure of educational attainment and determine some of the possible causes of any adverse outcomes, standardized neuropsychological tests were administered to both subjects and sibling controls when available. To assess the impact of childhood seizures on educational outcomes, those subjects with one seizure were compared to those with two or more seizures. The following neuropsychological tests were administered based on age: Wide Range Achievement Test-3 (WRAT-3), Test of Non-Verbal Intelligence-II (TONI-II), Wechsler Intelligence Scale for Children-III (WISC-III) or Wechsler Adult Intelligence Scale-revised (WAIS-III), and Conners' Continuous Performance Test 2nd edition (CPT). The WRAT-3 provides objective information about the level of educational attainment in reading, spelling, and mathematical computation, and was the primary outcome measure of the analysis. Given that there is considerable disparity in actual learning achievement from school district to school district, assessing educational achievement by tallying years of school completed (grade equivalents) has been shown to be markedly unreliable (Reynolds & Wilson, 1984; Kaufman et al., 1988). The reading recognition portion of the test has been shown to be more sensitive to actual ability than grade equivalents (Reynolds, 1989). The TONI-II provides a measure of overall cognitive ability without requiring a language-based response, and has demonstrated high reliability when administered to Spanish-speaking subjects (Brown et al., 1990). Given that the study population

was derived from a racially and ethnically diverse, predominantly inner city population, the TONI-II would provide an additional culture fair measure of intellectual ability. The WISC-III and the WAIS-III are the most widely used measures of intellectual functioning in the world (Lezak, 1993). The WISC-III is designed for children from 6 to 16 years of age, and the WAIS-III is designed for individuals older than the age of 16 years. Due to time constraints we administered four subscales of the WISC or WAIS (Similarities, Vocabulary, Picture Completion, and Block Design), which can yield estimates of overall intelligence quotient (IQ), and became the basis for the now available WASI (Wechsler Abbreviated Scale of Intelligence) widely used in research settings. The mean score and standard deviation in WRAT-3 reading, TONI-II, and WISC-III/WAIS-III full-scale IQ are 100 ± 15, and these tests have been validated in multiple populations (Jastak & Jastak, 1984; Jastak & Wilkinson, 1984; Brown et al., 1990; Wechsler, 1991, 1997; Wilkinson, 1993). The CPT is a computer-administered test designed to measure multiple aspects of attentional capacity including arousal, vigilance, speed of response, as well as commission/omission errors. The false-positive and false-negative rates of diagnosis of attention deficit and hyperactivity disorder (ADHD) by CPT is 10–15%, using the overall index cut-off point of 6. This was validated in a study of 3,000 subjects (Connors, 1994). Children with attentional problems typically perform poorly on tests requiring vigilance or sustained attention, and the CPT was used to check for presence of attentional problems that may be partly responsible for poor educational attainment (Spreen et al., 1995; Masur & Shinnar, 2000).

Sibling controls

Sibling controls for the included sample were recruited 10 or more years later whenever available, and used as normal controls with the same genetic and demographic background. An eligible sibling control was a sibling age matched within 5 years, and without a history of seizures, mental retardation, cerebral palsy, or other known prior neurologic insult. If two or more siblings were eligible, the one closest in age was chosen. Paired analysis for siblings was not performed on final analysis, as sibling controls were available in only 24% of cases.

Analysis

The primary outcome was enrollment into special education services or grade repetition. The primary variable of interest was children with a single seizure, in comparison to children with epilepsy. Recurrent seizures were reported in 105 (41%) of 258 children, thereby meeting the definition of epilepsy. Of these, 22 children (9%) had ≥10 seizures. Although the total number of seizures was collected as a continuous variable, it was highly skewed to the left (less frequent seizures) and was, therefore, categorized into three groups (single seizure, 2–9 seizures, and ≥10 seizures). Descriptive analyses were performed on the following variables: age at the first seizure, age at interview, sex, primary language, number of seizures (1 vs. 2–9 vs. ≥10 seizures), history of status epilepticus, terminal remission, current and previous use of antiepileptic medication, etiology (idiopathic vs. cryptogenic), collapsed epilepsy syndrome, mother's educational level, WRAT-III reading score, TONI-II score, WISC/WAIS IQ score, and CPT index. Recurrence was defined as the occurrence of any unprovoked seizure more than 24 h after the initial seizure (Commission on Epidemiology and Prognosis, 1993). Terminal remission was defined as a child who is seizure free and off AEDs for at least 5 years as of the last follow-up. The mothers' educational level was categorized as ''not completed high school,'' ''completed high school: or ''Bachelor's Degree and above.'' Primary analysis focused on the comparison between the subjects who had single seizures in contrast with subjects with epilepsy. The subjects with single seizures were also compared to the sibling control group. Pearson's chi square test and Fisher's exact test were used for categorical variables. Student's *t*-test or analysis of variance (ANOVA) was used for continuous variables. Kruskal-Wallis rank test was used to calculate p-value instead of ANOVA for continuous variables when appropriate. Test for trends across ordered groups by Cuzick was used to assess the association between the number of seizures and outcomes. Logistic regression model on the outcome ''received special education service or repeated grade'' was used to investigate the relative contribution of the variables of interest. Variables in the model were chosen based on predetermined criteria of $p < 0.25$ in bivariate analysis and clinical relevance from the previous studies. The significance level was set as $p < 0.05$. All analyses were undertaken with STATA for Windows (StataCorp, College Station, TX, U.S.A.).

Results

Population characteristics

Of 328 subjects from the original cohort with a cryptogenic/idiopathic first seizure, 258 subjects (79%) and 78 sibling controls had sufficient cognitive outcome data to be included for this analysis. The median age of the 258 subjects at first seizure was 5.5 years [mean 6.6, standard deviation (SD) 4.9, range 1 month to 19 years] with a median follow-up of 16.3 years (mean 16.1, SD 2.2, range 10.1 to 20.4 years). The median age at last follow-up was 21.7 years (mean 22.7, SD 5.4, range 12.5 to 38.4 years). Of the 258, 57% were male, and English was a primary language in 93%. Maternal education was variable, with 32 mothers (15%) not completing a high school education, 124 (58%) graduating from high school, and 59 (27%) with a Bachelor's Degree or higher. Characteristics of seizures are shown in Table 1. There was no difference in ethnicity

Table 1. Seizure characteristics

		Structured interview done		Neuropsychological tests done	
	All eligible case	Case (%)[a]	Case with sibling controls (%)[a]	Case (%)[a]	Case with sibling controls (%)[a]
N	328	258 (79)	78 (24)	162 (49)	44 (13)
Age at first seizure (median in year)	5.4	5.5	5.5	5.5	5.5
No. of seizures					
Single	200	153 (77)	44 (22)	94 (47)	21 (11)
2–9	106	83 (78)	28 (26)	52 (49)	17 (16)
≥10	22	22 (100)	6 (27)	16 (73)	6 (27)
Status epilepticus in past	46	40 (87)	14 (30)	25 (54)	10 (22)
Final seizure outcome					
≥5 year seizure free, off AEDs	284	233 (90)	70 (25)	142 (50)	39 (14)
≥5 year seizure free, on AEDs	26	13 (82)	4 (15)	7 (27)	3 (12)
Currently on AEDs	26	24 (92)	6 (23)	17 (65)	4 (15)
Ever been on AEDs	63	60 (95)	18 (29)	54 (86)	14 (22)
Idiopathic etiology	75	62 (83)	17 (23)	41 (55)	11 (15)
Collapsed epilepsy syndrome[b]					
BECCT/BOE[c]	44	36 (82)	10 (23)	24 (55)	5 (11)
Primary generalized epilepsy	31	25 (81)	7 (23)	17 (55)	6 (19)
Other focal epilepsy	122	92 (75)	30 (25)	57 (47)	17 (14)
Undetermined focal and/or generalized	131	106 (81)	31 (24)	64 (49)	16 (12)

[a]Divided by the number of eligible cases.
[b]Child with a single seizure was classified based on the characteristic EEG features (Shinnar et al., 1999).
[c]Benign childhood epilepsy with centrotemporal spikes/Benign childhood epilepsy with occipital spikes.

(p = 0.21) or mothers' educational level (p = 0.65) between 180 subject without available siblings and 78 subjects with available siblings.

Educational outcome

Among children in this cohort, 43 (28%) of 153 children with a single seizure and 42 (40%) of 105 children with epilepsy received special education services or repeated the grade (p = 0.05). Among the sibling controls, 19 (24%) of 78 received special education services or repeated a grade. Educational outcomes are summarized in Table 2. The epilepsy group as a whole had worse educational outcomes, when compared with sibling control (p = 0.03) or single seizure group (p = 0.05). Within the epilepsy group, children with ≥10 seizures received special education services or repeated a grade more often than children with 2–9 seizures (14/22, 64% vs. 28/83, 34%). There was a statistically significant trend in which the children with more seizures received special education or repeated grade more often (p = 0.004).

Neuropsychological outcome

Standardized neuropsychological tests were completed in 162 (63%) of 258 subjects and 46 of 78 sibling controls. Some subjects who have participated in the structured interview by phone, declined to come in for the full neuropsychological tests. Compared to subjects who did not complete neuropsychological testing, the subjects who completed testing were significantly more likely to be receiving special education or require repeating a grade (38% vs. 25%, p = 0.03). They were significantly more likely to have been placed on AEDs in the past (34% vs. 6%, p < 0.001). The mean age at the last follow-up (p = 0.29), total number of seizures (p = 0.59), current use of AEDs (p = 0.24), remission (p = 0.11), and mothers' education level (p = 0.44) were not statistically significantly different between the children who completed neuropsychological tests and those who did not. Table 2 shows the results of the neuropsychological test scores among the children with a single seizure, 2–9 seizures, and ≥10 seizures. Among the children, 51 subjects (31%) were younger than 16 years of age (34 in single seizures, 12 in 2–9 seizures, and 5 in ≥10 seizures). There were 9 (17%) of 43 children with 2–9 seizures and 8 (50%) of /16 children with ≥10 seizures who were currently on AEDs. Not surprising in a cryptogenic/idiopathic group with relatively mild epilepsy, only three children had IQ less than 70 (1 child in each group). Children with single seizures tended to score higher than children with epilepsy on WRAT reading (p = 0.08), TONI-II (p = 0.02), and WISC/WAIS (p = 0.07). There was an inverse trend between the number of seizures and test scores in WRAT reading (z = 0.04), TONI-II (z = 0.10), and WISC/WAIS (z = 0.09) but not in CPT (z = 0.62). There was no statistically significant difference in test scores between children with a single seizure versus controls.

The abbreviated versions of the WISC and WAIS did not allow for separate estimates of verbal and performance IQ. However, upon examining the vocabulary subscore of the WISC/WAIS, no difference was noted among the groups. The TONI-II, an estimate of nonverbal intelligence, did

Table 2. Standardized neuropsychological test scores and educational outcomes

Test	Siblings N = 46	Subjects all N = 164	p- value	Siblings N = 46	Single N = 95	Epilepsy N = 69	p-value			Number of seizures			z value for trend
							Siblings vs. Single	Siblings vs. Epilepsy	Single vs. Epilepsy	1 N = 95	2–9 N = 53	≥10 N = 16	
Age at test	19 ± 6	19 ± 5	0.37	19 ± 6	19 ± 5	20 ± 5	0.63	0.21	0.30	19 ± 5	20 ± 5	19 ± 5	
WISC/WAIS IQ	94 ± 14	95 ± 13 (161)[a]	0.58	94 ± 14	97 ± 13	93 ± 13 (66)[a]	0.25	0.70	0.07	97 ± 13	94 ± 12 (51)[a]	92 ± 16 (15)[a]	0.09
CPT													
Median	5.6	4.5 (162)[a]	0.86	5.6	5.1 (94)[a]	4.5 (68)[a]	0.95	0.76	0.82	5.1 (94)[a]	4.5	9.0 (15)[a]	0.65
Index ≥ 6	43%	46%	0.79	43%	46%	46%	0.80	0.82	0.45	46%	42%	60%	0.62
TONI-II Mean	91 ± 14	94 ± 15 (163)[a]	0.22	91 ± 14	96 ± 15 (94)[a]	91 ± 14	0.05	0.98	0.02	96 ± 15 (94)[a]	90 ± 13	92 ± 16	0.10
WRAT reading	92 ± 16	93 ± 16 (162)[a]	0.77	92 ± 16	95 ± 16 (94)[a]	90 ± 16 (68)[a]	0.36	0.55	0.08	95 ± 16 (94)[a]	92 ± 15 (52)[a]	85 ± 18	0.04
Received SE[b] or repeated the grade	19/78 (24%)	85/258 (33%)	0.15	19/78 (24%)	43/153 (28%)	42/105 (40%)	0.54	0.03	0.05	43/153 (28%)	28/83 (34%)	14/22 (64%)	0.004

[a]Number of subjects when it is different from the number on the first row.
[b]Special education service.

show an effect as noted previously (p = 0.02). However, the estimates of verbal IQ should be viewed with caution as based on only one subscale. We did separately examine the effect of age of onset on outcome and there was no difference in any outcome measure between subjects with age at first seizure ≤ 6 and those with age at first seizure >6, either in the overall group, those with a single seizure, or those with epilepsy.

Logistic regression model

Table 3 shows the result of bivariate analysis. The variables of interest are sex, the age at the first seizure, the age at last follow-up, the number of seizures, attainment of terminal remission, current use of AEDs, etiology, and mothers' education level. The mothers' education level was dichotomized as "not graduated from high school" and "graduated from high school." The logistic regression was performed focused on a subgroup of children with single seizure versus children with epilepsy, using the variables in bivariate analysis. Attainment of terminal remission and current use of AEDs were removed from the model, as they were not independent from number of seizures. When adjusted for sex, age at first seizure, age at last follow-up, and mothers' education level, patients with epilepsy were more frequently receiving special education services or repeating grades [p = 0.04, odds ratio (OR) 1.9; 95% confidence interval (CI) 1.0–3.5]. The results of logistic regression comparing the children based on the number of seizures reported the OR for enrollment into special education or repeating grades increased from 1.0 in children with a single seizure, to 2.0 in children with 2–9 seizures, and to 4.6 in children with ≥10 seizures.

Discussion

In this prospective cohort of children identified at the time of their first unprovoked seizures with a median follow-up period of 15 years, >50% of children had standardized neuropsychological testing. There was a statistically significant trend in which the children with more seizures tended to require special education or repeat a grade more often. The interpretation of this inverse trend needs caution, as this may simply indicate that the subjects with more seizures have more underlining brain dysfunction. Previous studies have reported lower cognitive test results in people with childhood-onset epilepsy, with approximately 30% of children in these studies classified as mentally retarded (Ellenberg et al., 1984; Murphy et al., 1995). These studies focused solely on children with epilepsy, often skewed by the children with severe epilepsy, and it was difficult to separate impact of seizures from other variables. Our cohort provided a unique opportunity to assess the impact of seizures in childhood on educational and cognitive function, as a majority of the children are not taking AEDs at present and had only one seizure, or had mild epilepsy. This cohort

Table 3. Result of bivariate analysis for educational outcome

	Received special education service or repeated grade		
	Never (n = 173)	Yes (n = 85)	p Value
Male sex	95 (65%)	52 (35%)	0.34
Age of first seizure in years, median (mean)	5.9 (6.9 ± 5.1)	4.6 (6.2 ± 4.5)	0.24
Age at last interview in years, median (mean)	22.0 (23.2 ± 5.5)	21.1 (21.9 ± 4.9)	0.06
# of seizures			
Single (%)	110 (72)	43 (28)	0.004
2–9 (%)	55 (66)	28 (34)	
≥10 (%)	8 (36)	14 (64)	
Attained terminal remission[a]			
Yes (%)	160 (69)	72 (31)	0.05
No (%)	13 (50)	13 (50)	
Currently on AED			
No (%)	160 (68)	75 (32)	0.26
Yes (%)	13 (57)	10 (43)	
History of status epilepticus			
No (%)	149 (68)	70 (32)	0.43
Yes (%)	24 (62)	15 (38)	
Etiology			
Cryptogenic (%)	132 (67)	65 (33)	0.98
Idiopathic (%)	41 (67)	20 (33)	
Mother's education level			
Not graduated HS[b] (%)	19 (59)	13 (41)	0.26
Graduated HS (%)	78 (63)	46 (37)	
BA[c] and above (%)	48 (81)	11 (19)	

[a]Seizure free for equal or greater than 5 years and off AEDs.
[b]High school.
[c]Bachelor's degree.

also has the strong advantage of well-screened epilepsy syndromes based on prospective long follow-up from the first seizure episode, as well as continuous EEG and MRI studies. The test results confirmed normal cognitive function in a majority of children regardless of the total number of seizures, yet children with single seizures tended to score higher than children with epilepsy. The results suggest that the children with a single seizure represent a group that is distinctly different from children with epilepsy. Austin et al. (2002) prospectively studied behavioral problems in 224 children with new-onset seizures (73% of them had recurrent seizures) and 159 siblings. The authors found statistically significant difference on Child Behavior Checklist (CBCL) Total and Internalizing Behavior Problems scores, with higher scores for children with epilepsy than for children with single seizures. Siblings had significantly lower Total and Internalizing Problems scores than both groups. Putting these results with those of the current study, there is further justification for defining epilepsy as greater than or equal to two seizures in view of cognitive comorbidity.

The reasons are unclear for the difference between subjects who completed neuropsychological testing and subjects who did not complete the tests. Those children with history of having been placed on AEDs might have been more motivated to continue in the study, and their parents might have worried more about the possibility of cognitive impairment. The overall mean scores for the neuropsychological tests in our subjects were lower than for the general population, but were nevertheless generally consistent with available sibling controls. The difference in each test score (WISC/WAIS IQ, TONI-II, WRAT reading) should not be interpreted as clinically meaningful based solely on the significance level ($p < 0.05$), as all groups had normal scores. Sibling controls were recruited as normal controls within the same genetic, socioeconomic status, and educational resources. Although we planned to perform matched-pair analysis between the subjects and their siblings, we decided against this strategy, as sibling controls were available in only 24% of cases and only 44 pairs of them completed the neuropsychological testing. The inclusion criteria for sibling control as having to be within 5 years difference from the subject might have decreased the eligibility of sibling controls. This age criterion was set to avoid the time effects, as demographics could change over 10 years. Nevertheless, we believe the sibling controls as a whole were a valid representation of our study population, and there was no significant difference in mothers' educational level or ethnicity between the subjects with sibling pairs and those without sibling pairs. The children with epilepsy required special education services or repeated the grade more often than the sibling controls. In contrast, the educational outcomes and standardized neuropsychological tests results for children

with single seizures were not significantly different from those of sibling controls. This indicates that one unprovoked seizure has little long-term impact on educational or cognitive activities. They do not seem to have same educational and cognitive problems as those reported in children with epilepsy.

Although the results of children with a single seizure in this study are valid, the results of children with epilepsy do not represent the spectrum of epilepsy of childhood onset. The educational and cognitive outcomes of childhood-onset epilepsy as a whole are better represented in other cohorts, such as the Connecticut cohort and the Finnish cohort (Sillanpaa et al., 1998; Berg et al., 1999). The nature of the current study design, which focused on a first unprovoked seizure, would exclude the children with myoclonic and/or absence seizures. Likewise, children with infantile spasms and Lennox-Gastaut syndrome were not eligible for inclusion into the original cohort. This limitation was unavoidable given the primary goal of studying the long-term effects of an isolated seizure or of a few seizures, as the above-mentioned syndromes often involve seizures that occur in clusters or with great frequency. As a result, children with epilepsy in this cohort represent biologically mild epilepsy, which would have biased our result toward not finding a difference. We did not observe the significant difference in CPT index, the test to assess the attention deficit-hyperactivity disorder (ADHD) symptoms between sibling controls, single seizure group, and epilepsy group. ADHD has been reported in children with epilepsy as a frequent comorbidity (Hermann et al., 2007). This could be related with the nature of the study design, which would exclude the children with absence epilepsy, in whom the ADHD is reported in 37% (Caplan et al., 2008).

Despite these caveats, our study demonstrates definitive neurocognitive and educational differences when comparing children with one seizure to those having even mild epilepsy. The reason that children with epilepsy required special education services or repeated grades more often than the children with single seizures certainly cannot be explained by the neuropsychological test scores. Academic underachievement in children with epilepsy independent from the seizure control has been well reported (Mitchell et al., 1991; Williams et al., 2001; Fastenau et al., 2008). Home environment, parental education, ADHD, and age of seizure onset have been found to be associated with academic underachievement. In our study, home environment and parental education were controlled by sibling controls, and the age of seizure onset was did not differ between the children with single seizure and the children with epilepsy. Our finding may indicate the presence of factors not measured in previous studies, such as labeling, stigma, and parental expectation. We were unable to determine if the school was informed about the seizure disorder, which might have influenced the educational placement. Our findings have potentially significant implications for the more comprehensive use of school assistive services early in the diagnosis of epilepsy, in hopes of preventing subsequent school failure.

Overall the study serves to both confirm the increasing data about cognitive and behavioral comorbidities in childhood-onset epilepsy and to emphasize that children with a single unprovoked seizure do appear to be a population distinct from those with epilepsy as defined by two or more seizures with respect to their comorbidities as well as their seizure outcomes.

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Disclosure

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. The authors declare no conflicts of interest.

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