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Epilepsy in Children With ADHD: A Population-Based Study

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Abstract

Prior studies suggest a higher incidence of symptoms of attention-deficit/hyperactivity disorder in children with epilepsy, but few have investigated epilepsy in children with attention-deficit/hyperactivity disorder. Our objective was to compare the incidence and characteristics of epilepsy among population-based, research identified cohorts of children with (N=358) and without attention-deficit/hyperactivity disorder (N=728), based on medical record review to age 20. Data abstracted included characteristics of seizures, testing, and treatment. Cases were 2.7 times more likely to have epilepsy than controls (95% confidence interval 0.94–7.76; p=0.066), had earlier seizure onset (median age 5.5 versus 15 years; p=0.020), and a trend toward more frequent seizures (more than monthly, 63% versus 17%). Among children with attention-deficit/hyperactivity disorder, those with epilepsy tended to be less likely to have received a clinical diagnosis of attention-deficit/hyperactivity disorder (63% versus 89%; p=0.052) or to be treated with stimulants (50% verses 85%; p=0.025). Our findings suggest a strong trend towards a higher incidence of epilepsy among children with attention-deficit/hyperactivity disorder compared to those without. Epilepsy in children with attention-deficit/hyperactivity disorder appears to be more severe than in those without. Finally, there appears to be a reluctance to diagnose and initiate treatment for attention-deficit/hyperactivity disorder in children with epilepsy.

Keywords

Attention-Deficit/Hyperactivity Disorder (ADHD); epilepsy; seizures; pediatric; epidemiology; stimulants

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BACKGROUND

Epilepsy and attention-deficit/hyperactivity disorder (ADHD) are both common childhood neurological disorders. Epilepsy, defined by two or more unprovoked, non-febrile seizures, affects up to 1% of children and adolescents, while the incidence of childhood ADHD is between 7.5–16% [1, 2]. The relationship between epilepsy and ADHD is complex and poorly understood. Previous epidemiological studies have shown significantly more inattention, hyperactivity and impulsivity in children with epilepsy compared to controls [3, 4]. Studies in pediatric epilepsy have found a 2.5 to 5.5-fold-increased risk of ADHD compared to healthy controls [5, 6, 7, 8]. Although the presence of ADHD in children with epilepsy is widely acknowledged, the risk of seizures in children with ADHD is less clear. The three small, uncontrolled studies that have examined the occurrence of seizures in select ADHD populations suggest between 2% and 7% of children with ADHD have epilepsy [9, 10, 11].

The purpose of our study was to estimate the incidence of epilepsy among children with ADHD compared to children without ADHD in a population-based sample of children. We also compared the characteristics of epilepsy in children with and without ADHD.

METHODS

Study Setting

Cumulative school records for every child born in Rochester, Minnesota between January 1, 1976 and December 31, 1982 to mothers residing in Independent School District #535 (Rochester, Minnesota) were available through a contractual research agreement. Children who were ever enrolled at any of the district's public, private or parochial schools as well as children who were home-schooled were included in our study. School cumulative records include the results of all standardized tests, absenteeism data, yearly report cards, Individualized Educational Program plans, and graduation status. Through the Rochester Epidemiology Project, we also had access to the complete medical records of all members of the birth cohort [12, 13]. These medical records are available from the Mayo Clinic, Olmsted Medical Center, and the few private medical practitioners in the community, encompassing essentially all of the providers of primary and specialty medical care for Rochester residents. Through the Rochester Epidemiology Project, all inpatient and outpatient diagnoses are indexed for computerized retrieval (medical diagnostic index) [13]. The medical records contain a detailed history of all medical encounters in the community including ambulatory medical and social services, hospitalizations, emergency department visits, laboratory and imaging tests, and psychiatry and psychology reports and test results, from birth until the patient no longer resides in the community.

Subjects

Subjects for this study include 5,718 members of the 1976–1982 Rochester birth cohort. Detailed descriptions of this population and methods for deriving the incidence of ADHD have previously been published and are summarized below as they apply to this study [12, 14]. This study was approved by the Mayo Clinic Institutional Review Board.

Identification of ADHD Incident Cases and Non-ADHD Controls

To identify incident cases of ADHD, we employed a five-step approach. First, we reviewed the school records for all 5,718 subjects for evidence of any concern about learning or behavior. Second, for all subjects with any type of learning or behavioral concern identified in the school records (n=1951), we searched for additional information from school and medical records, including symptoms of ADHD as specified in the Diagnostic and Statistical

Manual of Mental Disorders, Fourth Edition, results from teacher and/or parent ADHD questionnaires, clinical diagnoses of ADHD, and documentation of treatment with medication commonly prescribed for ADHD [12]. Third, among the subjects whose school records did *not* include any suggestion of learning or behavioral problems (n=3767), we searched the Medical Diagnostic Index for diagnoses related to or including ADHD. Fourth, we reviewed the records of birth cohort members who had received care at the only private community provider of psychiatric care other than Mayo Clinic or the Olmsted Medical Center and identified four additional potential ADHD cases. Finally, in the fifth step, we applied explicit research criteria to identify ADHD cases among the 1,344 possible cases identified in the preceding four steps. Specifically, a research diagnosis of ADHD required at least two of the following three factors: 1) documented symptoms that fulfill diagnostic criteria for ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, 2) positive results on ADHD questionnaires, and 3) documented clinical diagnosis of ADHD. As per accepted diagnostic criteria, we excluded cases who had a diagnosis of pervasive developmental disorder, severe mental retardation (Intelligence Quotient < 50), schizophrenia, or other psychotic disorder [15].

For each of the ADHD cases, two controls without ADHD were selected from the same birth cohort. Before matching we excluded potential controls who had a diagnosis of severe mental retardation, pervasive developmental disorder, or any major psychiatric disorder as these diagnoses also excluded cases. Controls were matched on gender and date of birth (± 6 months). Among 379 research-identified ADHD cases and 758 matched controls without ADHD, 21 cases and 30 controls were excluded from further study in accordance with Minnesota state law because they denied authorization for use of their medical records for research purposes. Therefore the study sample consisted of 358 ADHD cases and 728 controls. All of the cases and controls were followed from birth up to the date of last medical follow-up prior to their 20th birthday.

Review of Medical Records for Documentation of Seizures and Epilepsy

All ADHD cases and controls were screened for medical diagnostic index codes that potentially could indicate a history of seizure activity (Table 1). The medical records of those with a positive screen were reviewed to determine if they had suffered febrile, other provoked, or unprovoked seizures before age 20. A pediatric epileptologist (ECW) reviewed the medical records of all potential seizure cases. Seizure type and epilepsy syndromes were identified if classifiable based on information documented in the medical record. The following data were recorded: dates and descriptions of seizures, predisposing causes of seizures, neurological examination, electroencephalography and brain imaging data, treatment, family history of seizures, and measures of epilepsy severity including frequency of seizures.

For ADHD cases, the following variables were collected: date diagnostic criteria for ADHD were met, stimulant medications prescribed, and results of cognitive testing (primarily Wechsler Intelligence Scale for Children). Full-scale Intelligence Quotient scores were collected for both first testing after age six and last testing prior to age 19. We were unable to definitively establish ADHD subtype on the basis of medical and school records.

Definitions

For study purposes, the following definitions were applied.

Febrile seizure: a seizure occurring between six months and six years of age during a febrile illness with a body temperature of 38.5 degrees Celsius or higher, without evidence of an intracranial infection.

Atypical febrile seizure: febrile seizure with evidence of focality, duration longer than 15 minutes, or occurring more than once in a 24-hour period.

Other provoked seizure: seizure occurring in close temporal association (within seven days) of an acute structural, systemic, metabolic, or toxic insult to the central nervous system.

Unprovoked seizure: seizure occurring in the absence of any acute identifiable cause. *Epilepsy*: two or more unprovoked seizures at least 24 hours apart.

Refractory epilepsy: failing more than two antiepileptic medication for lack of efficacy after adequate trial of appropriate medication and still having seizures within the last year of follow-up.

Abnormal neurological exam: any global or focal findings on examination by a neurologist at time of diagnosis of first seizure, excluding those present solely in the postictal state.

Abnormal Electroencephalography (EEG) background: Background slowing on more than half of all EEG records performed on a given subject.

Statistical Analyses

The cumulative incidence of febrile seizure, other provoked seizure, single unprovoked seizure, and epilepsy was calculated using the Kaplan-Meier method. Cox proportional hazards models were fit to estimate the risk ratios (cases versus controls) and corresponding ninety-five percent confidence intervals (95% confidence interval). All calculated p-values were two-sided and p-values less than 0.05 were considered statistically significant. Analyses were performed using the version 9.1 SAS software package (SAS Institute, Inc., Cary, NC).

RESULTS

Clinical data were available to age 20 for 81.3% of the 358 ADHD cases and 75.7% of the 728 controls with a mean age at last follow-up 19.2 years for cases and 18.9 years for controls. Seventy-five percent of subjects in each group were male. Of the 1086 cases and controls, screening the medical diagnostic index for potential seizure history yielded positive screens in 105 ADHD cases and 143 controls. Upon subsequent review of the medical records for these individuals, a seizure history was found to be present in 23 cases and 32 controls. The cumulative incidence of epilepsy, single unprovoked seizures, febrile seizures, and other provoked seizures among cases and controls is shown in Table 2.

Cases and controls did not differ in the incidence of single unprovoked, febrile, or other provoked seizures. Among subjects with febrile seizures, atypical features were not more common in cases (44%, 4/9) than in controls (38%, 6/16).

ADHD cases were 2.7 times more likely to have epilepsy than controls, although this association did not reach statistical significance (p=0.066, 95% confidence interval 0.94 – 7.76). Seizure onset occurred prior to age 10 in all of the children with epilepsy in the ADHD group, while two of the six controls with epilepsy had seizure onset after age 18. Secondary analysis with follow-up censored at 18 years instead of 20 years yielded improved follow-up (89% of cases, 88% of controls) and individuals with ADHD were 4.1 times more likely to have epilepsy than controls (p=0.022, 95% confidence interval 1.23 – 13.52). Since epilepsy may be more common among children with mild mental retardation we performed a separate secondary analysis removing all children with an intelligence quotient < 70 and/or cerebral palsy (n=3) from our original dataset and ADHD cases were

still 2.4 times more likely to have epilepsy than controls, although this association did not reach statistical significance (p=0.121, 95% confidence interval 0.80 – 7.04).

Characteristics of Epilepsy Among Children with and without ADHD

We performed additional exploratory analysis of the characteristics of epilepsy in ADHD cases and controls (Table 3). The epilepsy syndromes in ADHD cases included childhood absence epilepsy (N=2), juvenile myoclonic epilepsy (N=1), epilepsy with generalized tonic clonic seizures on awakening (N=1), undefined generalized epilepsy (N=1) and localization related epilepsy (N=3, one symptomatic with Sturge-Weber syndrome and two cryptogenic). Syndromes for controls without ADHD included juvenile myoclonic epilepsy (N=2), undefined generalized epilepsy (N=2), and localization-related epilepsy (N=2, both cryptogenic).

In addition to having a younger age at epilepsy diagnosis (median age 5.5 versus 15 years, p=0.020), ADHD cases with epilepsy had a shorter time interval between first and second unprovoked seizures (median interval 1.6 versus 9.2 months). Epilepsy in ADHD cases had a higher seizure frequency in both the first year after epilepsy diagnosis as well as in the worst year. Half of cases versus only 17% of controls failed at least one antiepileptic medication for lack of efficacy, and one quarter of cases versus none of controls had refractory epilepsy at last follow-up. Five ADHD cases with epilepsy (63%) versus none of the controls were treated with phenobarbital, however in all cases phenobarbital was stopped prior to the diagnosis of ADHD. Four of the five children were started on phenobarbital before age 5, so this difference may simply reflect the younger age at seizure onset in the ADHD cases as phenobarbital has traditionally been used most commonly in neonatal and infantile-onset seizures. The median duration of treatment with phenobarbital was 2.1 years (range 2 weeks to 4.7 years). Two of the ADHD cases had epilepsy surgery (one achieving seizure freedom) and one was treated with a vagal nerve stimulator; none of the control subjects underwent these procedures.

Characteristics of ADHD in Children with and without Epilepsy

Among the children who met research criteria for ADHD, only five of the eight (63%) with epilepsy had a clinical diagnosis of ADHD on record compared to 312 of the 350 (89%) of children without epilepsy (p=0.052, Fisher’s exact test). Research-determined age of ADHD diagnosis did not differ between children with and without epilepsy (median age 7.8 versus 9.7 years, p=0.47, Wilcoxon rank sum test). All children with comorbid epilepsy and ADHD had seizure onset prior to research-identified ADHD diagnosis. However, the date of research diagnosis of ADHD that we determined is unlikely to reflect when ADHD symptoms first began. Stimulant medication was used to treat ADHD in 85% (297/350) of the children without epilepsy but only 50% (4/8) of the children with epilepsy (p=0.025). Cognitive testing results were available for all ADHD subjects with epilepsy and 87% (N=305) of ADHD subjects without epilepsy. Six of eight epilepsy cases and 182/305 non-epilepsy cases had cognitive testing on at least two occasions. Although our numbers are small, there is a trend toward a greater decline in cognitive function over time in the cohort with epilepsy. Results are presented in Table 4.

DISCUSSION

In this population-based cohort study we found a strong trend toward a higher incidence of epilepsy among children with ADHD than among controls without ADHD (hazard ratio 2.7, confidence interval 0.9–7.7). To our knowledge this is the first population-based case/control study of epilepsy among ADHD incidence cases indentified from the same birth

cohort. We found no differences in incidence of febrile seizures, other provoked seizures, or single unprovoked seizures between the groups.

This study expands upon three studies that also found an increased incidence of epilepsy in subsets of ADHD patients, but adds the strengths of a control group and a large population-based sample without referral bias [9, 10, 11]. From the largest of these studies, Williams and colleagues described parental-reported presence of epilepsy among children with ADHD seeking care at a developmental center to be around 2%, almost identical to our finding of 2.2% despite differences in methodology and study groups [10]. However, they proposed that the higher incidence of epilepsy could be attributed to the comorbid presence of other neurodevelopmental disorders including cerebral palsy, pervasive developmental disorders, and developmental delay. In our study we excluded children with pervasive developmental disorders. Additionally, the trend toward epilepsy among ADHD children persisted even after exclusion of children with mild mental retardation or cerebral palsy. Our findings therefore suggest that the observed higher incidence of epilepsy among children with ADHD is not an artifact. Furthermore, a link between epilepsy and ADHD has previously been established. Austin and colleagues demonstrated significantly more attention problems in children prior to their first recognized seizure compared to siblings without seizures, and a population-based study in Iceland found a history of ADHD was 2.5 times more likely in new cases of epilepsy than a control group without epilepsy [8, 16]. It is likely that there is a common neurobiological predisposition for both a lower seizure threshold and ADHD behaviors that may involve both genetic and environmental factors. Indeed, studies using a mouse model suggest that animals with a lower genetic seizure threshold have greater impulsivity and hyperactivity prior to developing seizures [17, 18]. Another possibility is that one disorder or its treatment causes the other. Status epilepticus, frequent seizures, or frequent interictal epileptiform discharges have been associated with cognitive impairment [19, 20]. Additionally, antiepileptic medications, particularly barbiturates, benzodiazepines and levetiracetam are recognized to have cognitive and behavioral side effects that may resemble symptoms of ADHD [21]. Theoretically, ADHD may result in a lower seizure threshold due to increased head injury or use of stimulant medication. However, our study findings do not support this as significant head injury was uncommon and seizure onset occurred prior to diagnosis or treatment of ADHD among our patients. The relationship of these two disorders is complex, and our study provides a supplementary perspective to improve understanding of this relationship.

Epilepsy in children with comorbid ADHD appears to be more severe than in those without ADHD. Children with ADHD in our study had earlier seizure onset, faster progression to epilepsy, and greater seizure frequency. Status epilepticus was more common, seizures were less likely to respond to antiepileptic medication, and epilepsy was more likely to be refractory in those with ADHD. Children with epilepsy and ADHD were also more likely to have an abnormal neurological examination and abnormal background rhythm on EEG, possibly reflecting greater underlying neurological dysfunction. Both neurological exam and EEG abnormalities have been reported in children with ADHD [22, 23]. These findings are consistent with previous literature suggesting ADHD may be a marker of a unique subset of children prone to have a more severe, difficult to treat epilepsy compared to childhood epilepsy as a whole [24]. However, our numbers are small as reflected by the lack of identifying any cases in our sample with Benign Epilepsy with Centrotemporal Spikes despite the overall high frequency of this type of epilepsy in childhood epilepsies. Therefore, these conclusions are speculative and further studies are needed in children with both epilepsy and ADHD to better define possible subgroups that could have implications for clinical management.

We did not observe a difference in age of research diagnosis of ADHD between children with and without epilepsy, however there was a tendency for children with epilepsy to be less likely to have a clinical diagnosis despite positive questionnaires and documentation of fulfillment of all criteria for ADHD in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition ($p=0.051$). Children with epilepsy and ADHD were also less likely to be treated with stimulant medications than children with ADHD who did not have epilepsy. Not simply relying on a clinical diagnosis of ADHD is a strength of our study design, allowing identification of all children with ADHD, regardless of comorbid conditions that should not exclude a diagnosis of ADHD. Our findings may suggest a hesitation to diagnose symptoms of inattention, hyperactivity, and impulsivity as ADHD in childhood epilepsy, as well as a reluctance to treat those prone to seizures with stimulant medication. However, clinical guidelines support the use of stimulant medications for children with epilepsy and ADHD as the benefits outweigh the potential risks [25]. Failure to recognize and treat true symptoms of ADHD in children with or without epilepsy leaves these children at risk for lifelong academic, social, and behavioral problems [26].

Although all of our patients with both epilepsy and ADHD had seizure onset before ADHD diagnosis we cannot assess the temporal relationship of these two disorders given the difficulty in determining when symptoms of ADHD first began based on school records beginning at age five. Some studies suggest ADHD behaviors may predate seizure onset, but more prospective studies need to be conducted to investigate the temporal relationship between ADHD and epilepsy further [16]. We also looked at cognitive function among those with prior testing. Our findings suggest greater cognitive impairment in children with both epilepsy and ADHD than in children with ADHD alone. Previous research has suggested children with Rolandic spikes and ADHD perform worse on several neuropsychological domains, specifically response inhibition [27]. This is consistent with the proposal of a more severe underlying brain dysfunction in children with both epilepsy and ADHD [24]. However, this needs to be confirmed in larger studies.

Potential limitations of our study included our reliance on diagnostic codes in the medical records to screen for seizure activity. However, our broad range of diagnostic codes and the natural history of epilepsy involving multiple episodes reduce the likelihood any epilepsy cases were unrecognized. The size of our study was only large enough to show trends rather than statistically significant results. Additionally, the generalizability of these results is limited as Rochester is a primarily white, middle class community. Nevertheless, these data provide much needed baselines for comparison with other populations. Specific strengths unique to our study include its population-based birth cohort design and intensive evaluation for ADHD. With these strengths and limitations in mind we feel the descriptive information we present in this paper is an important addition to understanding the relationship between these two common childhood disorders.

In conclusion, to our knowledge this is the only population-based case/control study of epilepsy among children with ADHD. We found a 2.7 fold greater incidence of epilepsy among children with ADHD than in controls. The epilepsy in children with ADHD appeared to have an earlier onset, greater severity, and was less likely to respond to antiepileptic medications. Among children with ADHD symptoms, those with epilepsy were less likely to receive a clinical diagnosis and treatment of ADHD than those without, possibly reflecting a reluctance to diagnose and treat ADHD symptoms in children with epilepsy.

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Abbreviations

ADHD	attention-deficit/hyperactivity disorder
EEG	electroencephalography

References

1. Sander JW. The epidemiology of epilepsy revisited. Curr Opin Neurol. 2003:165–170. [PubMed: 12644744]
2. Barbaresi WJ, Katusic SK, Colligan RC, Pankratz VS, Weaver AL, Weber KJ, Mrazek DA, Jacobsen SJ. How common is attention-deficit/hyperactivity disorder? Incidence in a population-based birth cohort in Rochester, Minn. Arch Pediatr Adolesc Med. 2002:217–224. [PubMed: 11876664]
3. McDermott S, Mani S, Krishnaswami S. A Population-Based Analysis of Specific Behavior Problems Associated with Childhood Seizures. J Epilepsy. 1995:110–118.
4. Carlton-Ford S, Miller R, Brown M, Nealeigh N, Jennings P. Epilepsy and children's social and psychological adjustment. J Health Soc Behav. 1995:285–301. [PubMed: 7594360]
5. Dunn DW, Austin JK, Harezlak J, Ambrosius WT. ADHD and epilepsy in childhood. Dev Med Child Neurol. 2003:50–54. [PubMed: 12549755]
6. Hermann B, Jones J, Dabbs K, Allen CA, Sheth R, Fine J, McMillan A, Seidenberg M. The frequency, complications and aetiology of ADHD in new onset paediatric epilepsy. Brain. 2007:3135–3148. [PubMed: 17947336]
7. Davies S, Heyman I, Goodman R. A population survey of mental health problems in children with epilepsy. Dev Med Child Neurol. 2003:292–295. [PubMed: 12729141]
8. Hesdorffer DC, Ludvigsson P, Olafsson E, Gudmundsson G, Kjartansson O, Hauser WA. ADHD as a risk factor for incident unprovoked seizures and epilepsy in children. Arch Gen Psychiatry. 2004:731–736. [PubMed: 15237085]
9. Ishii T, Takahashi O, Kawamura Y, Ohta T. Comorbidity in attention deficit-hyperactivity disorder. Psychiatry Clin Neurosci. 2003:457–463. [PubMed: 12950698]
10. Williams J, Schulz EG, Griebel ML. Seizure occurrence in children diagnosed with ADHD. Clin Pediatr (Phila). 2001:221–224. [PubMed: 11336422]
11. Wisniewska B, Baranowska W, Wendorff J. The assessment of comorbid disorders in ADHD children and adolescents. Adv Med Sci. 2007:215–217. [PubMed: 18229669]
12. Katusic SK, Barbaresi WJ, Colligan RC, Weaver AL, Leibson CL, Jacobsen SJ. Case definition in epidemiologic studies of AD/HD. Ann Epidemiol. 2005:430–437. [PubMed: 15967390]
13. Melton LJ 3rd. History of the Rochester Epidemiology Project. Mayo Clin Proc. 1996:266–274. [PubMed: 8594285]
14. Katusic SK, Colligan RC, Barbaresi WJ, Schaid DJ, Jacobsen SJ. Potential influence of migration bias in birth cohort studies. Mayo Clin Proc. 1998:1053–1061. [PubMed: 9818038]
16. Austin JK, Harezlak J, Dunn DW, Huster GA, Rose DF, Ambrosius WT. Behavior problems in children before first recognized seizures. Pediatrics. 2001:115–122. [PubMed: 11134444]
17. Gilby KL, Thorne V, Patey A, McIntyre DC. Ruling out postnatal origins to attention-deficit/hyperactivity disorder (ADHD)-like behaviors in a seizure-prone rat strain. Behav Neurosci. 2007:370–379. [PubMed: 17469927]
18. McIntyre DC, Gilby KL. Genetically seizure-prone or seizure-resistant phenotypes and their associated behavioral comorbidities. Epilepsia. 2007:30–32. [PubMed: 18047598]
19. Aldenkamp A, Arends J. The relative influence of epileptic EEG discharges, short nonconvulsive seizures, and type of epilepsy on cognitive function. Epilepsia. 2004:54–63. [PubMed: 14692908]

20. Vlooswijk MC, Jansen JF, Reijs RP, de Krom MC, Kooi ME, Majoie HJ, Hofman PA, Backes WH, Aldenkamp AP. Cognitive fMRI and neuropsychological assessment in patients with secondarily generalized seizures. Clin Neurol Neurosurg. 2008:441–450. [PubMed: 18339478]

21. Bourgeois BF. Determining the effects of antiepileptic drugs on cognitive function in pediatric patients with epilepsy. J Child Neurol. 2004:S15–24. [PubMed: 15526967]

22. Barry RJ, Clarke AR, Johnstone SJ. A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. Clin Neurophysiol. 2003:171–183. [PubMed: 12559224]

23. Nass RD. Evaluation and assessment issues in the diagnosis of attention deficit hyperactivity disorder. Semin Pediatr Neurol. 2005:200–216. [PubMed: 16780291]

24. Sherman EM, Slick DJ, Connolly MB, Eyrl KL. ADHD, neurological correlates and health-related quality of life in severe pediatric epilepsy. Epilepsia. 2007:1083–1091. [PubMed: 17381442]

25. Dunn DW, Kronenberger WG. Childhood epilepsy, attention problems, and ADHD: review and practical considerations. Semin Pediatr Neurol. 2005:222–228. [PubMed: 16780293]

26. Smoot LC, Boothby LA, Gillett RC. Clinical assessment and treatment of ADHD in children. Int J Clin Pract. 2007:1730–1738. [PubMed: 17877659]

27. Holtmann M, Matei A, Hellmann U, Becker K, Poustka F, Schmidt MH. Rolandic spikes increase impulsivity in ADHD - a neuropsychological pilot study. Brain Dev. 2006:633–640. [PubMed: 16757138]

Table 1

Examples of diagnostic index codes

Clinical Diagnoses	Epilepsy, Seizure, Convulsion, Febrile convulsion Spells Syncope Encephalitis, Meningitis or other infection of the central nervous system Encephalopathy Pseudoseizure A disorder of consciousness Head trauma or Traumatic brain injury Central Nervous System neoplasm 3
Investigations	Brain imaging (any modality) Electroencephalography Neurology examination without a diagnosis
Other	All deaths of any cause

Table 2

Seizure diagnoses among cases and controls

Type of Seizure diagnosis	ADHD[1] cases (N=358)					Controls (N=728)					Risk Ratio (95% CI[2])	P value
	No.	Cumulative incidence by age, yrs (%)				No.	Cumulative incidence by age, yrs (%)					
		5	10	15	20		5	10	15	20		
Febrile	9	2.5	2.5	2.5	2.5	16	2.2	2.2	2.2	2.2	1.09 (0.46–2.57)	0.85
Other Provoked	5	0.6	0.8	0.8	1.4	6	0.4	0.6	0.8	0.8	1.68 (0.51– 5.50)	0.39
Single Unprovoked	1	0.3	0.3	0.3	0.3	4	0.3	0.3	0.6	0.6	0.5 (0.06– 4.51)	0.54
Epilepsy	8	1.1	2.0	2.3	2.3	6	0.1	0.1	0.4	0.9	2.7 (0.94–7.76)	0.066

[1] ADHD = Attention-Deficit/Hyperactivity Disorder

[2] CI = Confidence Interval

Table 3

Descriptive characteristics of epilepsy between the ADHD cases and controls

	ADHD[1] Cases (N=8)	Controls (N=6)
Age in years at epilepsy diagnosis, Median (range)	5.5 (0–10)	15 (2–18)
Abnormal baseline neurological examination	2 (25%)	0 (0%)
Abnormal background on electroencephalography	7 (88%)	1 (17%)
Months between first and second unprovoked seizure, Median (range)	1.6 (0–18.7)	9.2 (0–34.7)
Epilepsy Syndromes		
Idiopathic generalized	5 (63%)	4 (67%)
Symptomatic generalized	0 (0%)	0 (0%)
Idiopathic localization-related	0 (0%)	0 (0%)
Symptomatic localization-related	1 (13%)	0 (0%)
Cryptogenic localization-related	2 (25%)	2 (33%)
Seizures > monthly over first year of diagnosis	4 (50%)	1 (17%)
Seizures > monthly in worst year	5 (63%)	1 (17%)
History of status epilepticus	2 (25%)	1 (17%)
Family history of epilepsy	2 (25%)	2 (33%)
Number of children failing ≥1 antiepileptic medication for lack of efficacy	4 (50%)	1 (17%)
Number of antiepileptic medications failed due to lack of efficacy, Median (range)	0.5 (0–6)	0 (0–1)
Refractory epilepsy at follow-up	2 (25%)	0 (0%)

[1] ADHD = Attention-Deficit/Hyperactivity Disorder

Table 4

Cognitive testing in ADHD[1] subjects with and without epilepsy

	Epilepsy Median (Range)	No Epilepsy Median (Range)	P values[3]
Age at first testing	7.2 (6.0–18.8) (N=8)	7.8 (6.0–18.8) (N=305)	0.22
FSIQ[2] at first testing	94 (69–122)	101 (69–147)	0.17
Age at last testing	14.3 (11.0–18.4) (N=6)	12.7 (6.5–18.6) (N=182)	0.22
FSIQ at last testing	81 (56–99)	97 (59–142)	0.011

[1] ADHD = Attention-Deficit/Hyperactivity Disorder

[2] FSIQ = Full-Scale Intelligence Quotient

[3] Two-sided p-value based on Wilcoxon rank sum test