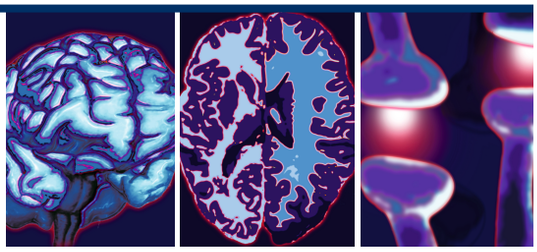
RESEARCH ARTICLE



Elevated rates of ADHD in mothers of children with comorbid ADHD and epilepsy

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Summary points

- ADHD and epilepsy are highly comorbid.
- Several mechanisms have been proposed to explain the comorbidity between ADHD and epilepsy.
- In this pilot study, the prevalence and severity of ADHD symptoms in mothers of children with comorbid ADHD and epilepsy were evaluated. In addition, the prevalence of ADHD in mothers with and without family members with a history of epilepsy, other than the index child, was assessed.
- A total of 50% of mothers met the DSM-IV criteria for ADHD. ADHD was more prevalent in mothers with a positive family history than in mothers without. Mothers with a positive family history had more hyperactivity symptoms, a higher ADHD severity and higher hyperactivity scores than mothers with a negative family history.

SUMMARY **Objectives:** To describe the prevalence of ADHD in mothers of children with comorbid ADHD and epilepsy (ADHD+E) and to compare ADHD symptoms in mothers with (Fam^+) and without (Fam^-) additional relative(s) with epilepsy. **Patients & methods:** Mothers (n = 16) of children with ADHD+E were assessed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Age Children ADHD module and the ADHD Rating Scale IV. Information was collected on the presence (Fam^+) or absence (Fam^-) of first- or second-degree relatives with epilepsy in the sample. **Results:** A total of 50% of mothers met the DSM-IV criteria for ADHD. ADHD was more prevalent in Fam^+ mothers (80%) compared with Fam^- mothers (36%; p = 0.14). Fam^+ mothers had more current hyperactivity symptoms than Fam^- mothers (p = 0.002), higher current ADHD severity (p = 0.02) and higher ADHD Rating Scale IV hyperactivity scores (p = 0.008). **Conclusion:** The prevalence of ADHD in mothers of children with ADHD+E is elevated in this pilot study, suggesting that ADHD symptoms in children with epilepsy and their mothers reflects shared familial genetic or environmental risks, potentially resulting in a higher prevalence of both disorders among family members. This is a pilot study and larger controlled studies are warranted.

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ADHD and epilepsy have prevalence rates in the general pediatric population of 3–7% and 0.5–1%, respectively [1–4]. However, the co-occurrence of these two disorders is high and the relationship appears to be bidirectional in nature. Individuals with ADHD are at an increased risk for the development of seizures [5–8], while patients with epilepsy have an increased prevalence of ADHD [9–12]. The prevalence of ADHD in patients with epilepsy is estimated to range from 12 to 39%, a several-fold increase from that seen in the general population [9–12]. Although a number of mechanisms have been proposed to explain the increased prevalence of ADHD in patients with epilepsy, the exact reasons are not fully understood. Some of the mechanisms described include: the effects of antiepileptic medications, adrenergic dysfunction, and the effects of chronic seizures and subclinical epileptiform activity on cognitive functions [13]. Another possibility is that a common genetic variant leads to neurodevelopmental vulnerability that increases risk in some families [13]. If so, the prevalence of ADHD should be increased in family members of children with comorbid ADHD and epilepsy (ADHD+E).

This latter possibility is explored in this pilot study by evaluating the prevalence and severity of ADHD symptoms in mothers of children with comorbid ADHD+E, and by comparing prevalence in mothers with (Fam^+) and without (Fam^-) family members with a history of epilepsy other than the index child. It is hypothesized that the observed prevalence of ADHD in these mothers would be higher than has been typically reported among mothers of children with ADHD without epilepsy. Furthermore, it is suggested that mothers who had more than one family member with epilepsy would have a higher likelihood of having ADHD, and the higher the number of family members affected, the more severe the ADHD symptoms would be.

Patients & methods

Participants

A total of 39 mothers of children who had been enrolled in a randomized, double-blind, placebo-controlled crossover trial of osmotic-release oral system methylphenidate were contacted and invited for an interview [14]. The primary inclusion criterion was being the mother of a child with a diagnosis of epilepsy who also had a diagnosis of ADHD confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Age Children – Epidemiologic Version (KSADS-E). Exclusion criteria were as follows: not the biological mother of the child; child had mental retardation; child had symptomatic epilepsy; and mother was diagnosed with seizures. Of the initial 39 mothers, 22 were eligible to participate, of whom 16 participated **(Figure 1)**. The study was approved by the Institutional Review Board of Boston's Children's Hospital (MA, USA), and informed consent was obtained per ethical standards.

A positive family history of epilepsy was defined as any history of idiopathic or cryptogenic epilepsy in a biological first- or second-degree relative of the mother (in addition to the index child with epilepsy). Five mothers had a positive family history of epilepsy (none of the affected relatives were siblings of the index child with epilepsy).

Fathers of the probands were also given the option of being interviewed. However, although data on fathers and siblings were collected, there was not enough data to run separate analyses. Thus, only data on mothers were analyzed. The demographic characteristics of these mothers are described in **Table 1**.

Measures

Psychiatric measures

KSADS-E

The KSADS-E was used to establish the diagnosis of ADHD. It is a widely used, standardized, semistructured psychiatric interview with well-established psychometric properties. It was designed for use in clinical and epidemiological research to assess past and current diagnoses of axis-I psychiatric disorders in children and adolescents. The ADHD module of the KSADS-E has been used extensively for research to assess past and current ADHD in adults [15–18]. The ADHD module of the KSADS-E was administered to the mothers in the study by a trained graduate student in clinical psychology, in person for one of the mothers and over the telephone for the other 15 mothers. The student was aware of the study's aims and hypothesis. The KSADS-E ADHD module enquires about the presence, in the past and currently, of each DSM-IV ADHD criterion. The diagosis of ADHD is then made using the instructions in the DSM-IV for applying the criteria (e.g., for criteria A, counting how many of the inattentive symptoms were present for at least 6 months, to a point that was inappropriate for the developmental level).

ADHD Rating Scale-IV Parent Version

The ADHD Rating Scale-IV (ADHD-RS) is a questionnaire that quantifies ADHD symptom severity over the preceding 6 months. It is an 18-item scale, each item corresponding to a DSM-IV ADHD symptom. The scale consists of four options: 0 = never or rarely; 1 = sometimes; 2 = often; and 3 = very often. The scale generates a hyperactivity score, an inattentive score and a total score. The scale has been used in ADHD research studies for different ages, including adults and both genders [19–22]. The ADHD-RS was administered by a trained graduate student in clinical psychology. The graduate student interviewed each mother about herself and rated symptom severity on each item based on the interview.

Statistical methods

The percentage of mothers with a DSM-IV diagnosis of ADHD was calculated. The prevalence of an ADHD diagnosis in mothers with and without a family history of epilepsy was compared using a Fisher's exact test, and group differences in numbers of symptoms were compared using independent samples t-tests (Statistical Package for Social Sciences, SPSS 16.0, IBM Corp., NY, USA).

Results

Eight mothers met the criteria for past or current diagnoses of ADHD. These included four out of five mothers with a family history of epilepsy, but only four out of 11 without such a history ($p = 0.14$) **(Figure 2)**. Six mothers in the study warranted both a past and current diagnosis. One mother met the criteria for current ADHD, but did not endorse a past ADHD diagnosis. Of the seven mothers warranting a current diagnosis of ADHD, five met the criteria for the predominantly inattentive type, two for the predominantly hyperactive–impulsive type and none for the combined type. Of the seven mothers with a past diagnosis of ADHD, three were inattentive, two were hyperactive–impulsive and two were the combined type.

The number of current hyperactive and current inattentive symptoms endorsed on the KSADS-E were tallied separately for the Fam$^+$ and Fam$^-$ mothers and the average number of each of these symptoms were compared between the groups. Fam$^+$ mothers reported more current symptoms of hyperactivity on the KSADS-E (mean: 5.4 ± 0.9; standard deviation [SD]: 1.4 ± 2.2; $t = -3.781$; $p = 0.002$). Although they also reported more current inattention symptoms, the difference did not achieve an accepted level of statistical significance (mean: 5.6 ± 2.9; SD: 2.9 ± 3.2; $t = -1.612$; $p = 0.13$).

Similarly, hyperactivity scores on the ADHD-RS were higher for Fam$^+$ mothers (mean: 11.4 ± 7.6; SD: 2.5 ± 4.3; $t = -3.065$; $p = 0.008$) and reached the trend level for inattention symptoms (mean: 13.8 ± 9.3; SD: 5.6 ± 7.5; $t = -1.899$; $p = 0.08$). The group difference was significant for the total score (mean: 25.2 ± 14.4; SD: 8.0 ± 10.3; $t = -2.738$; $p = 0.016$).

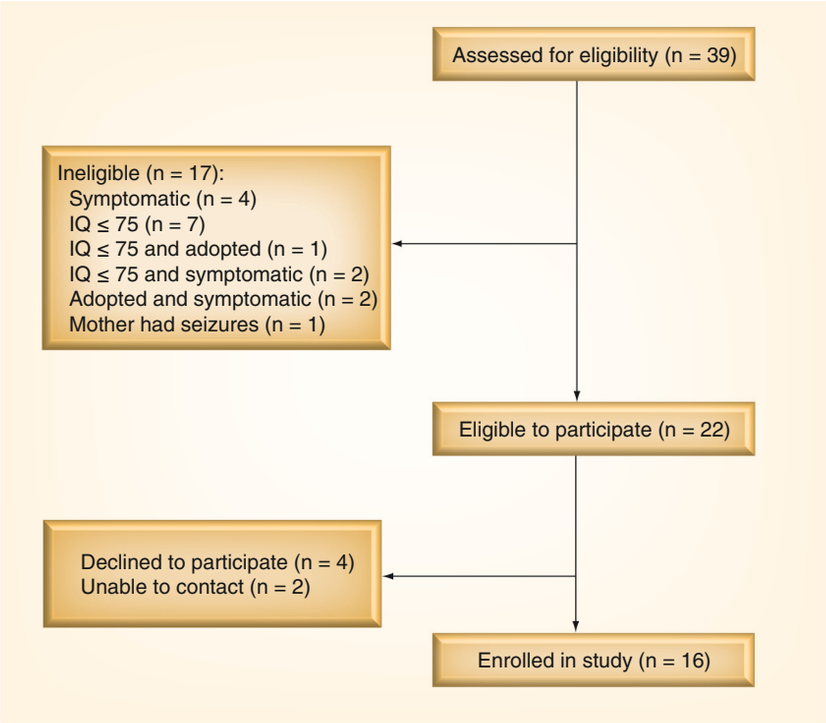

Figure 1. Selection of study subjects.
IQ: Intelligence quotient.

Table 1. Demographic characteristics of the 16 subjects (mothers of a child with ADHD and epilepsy).

Characteristic	Value
Age (years)	37–53 (mean 45 + 4.9)
Race	12 Caucasian, 2 African, 2 mixed
Ethnicity	13 non-Hispanic, 3 Hispanic
Child with focal onset seizures	12
Child with generalized onset seizures	4
Family history of epilepsy in first- or second-degree relative other than index child with epilepsy (none of the affected relatives were siblings of the index child with epilepsy)	5

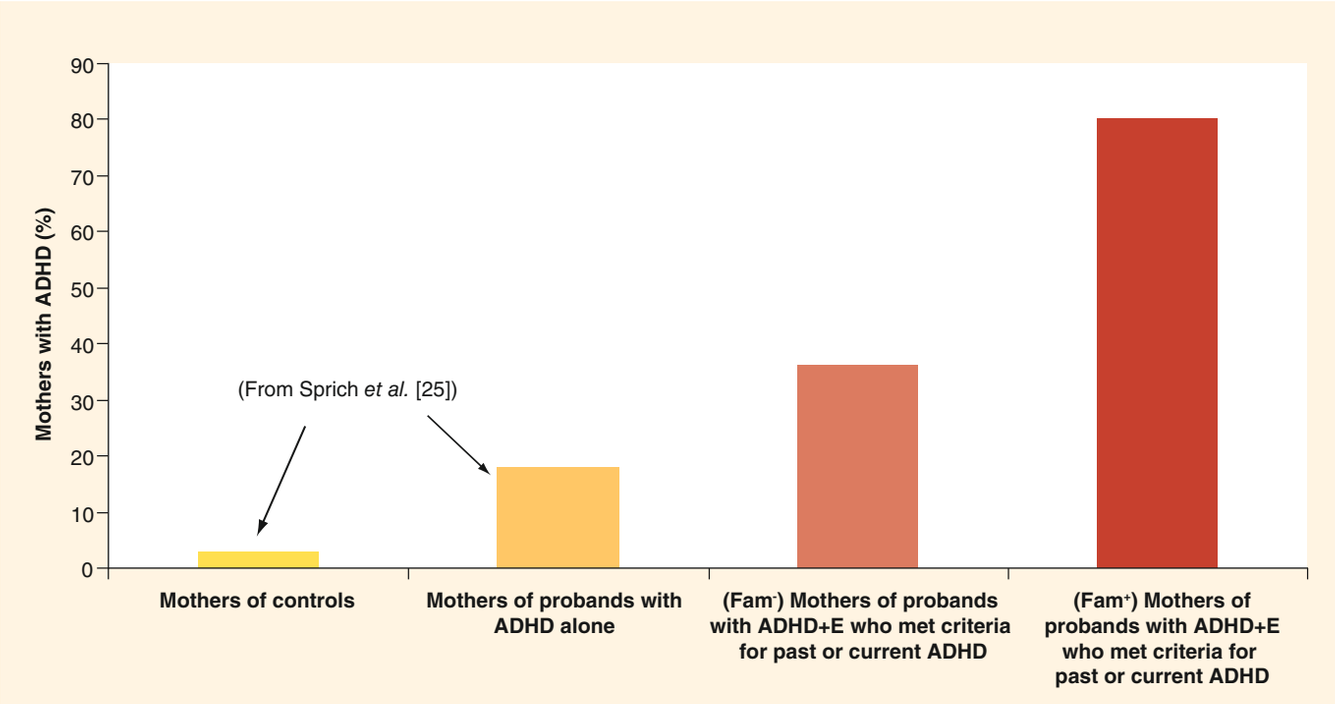

Figure 2. Rates of maternal ADHD. Study data compared to data described in Sprich *et al.* [25].
ADHD+E: Comorbid ADHD and epilepsy; Fam⁺: Mothers with family members with a history of epilepsy other than the index child; Fam⁻: Mothers without family members with a history of epilepsy other than the index child.

Among the children, 13 out of the 16 had idiopathic epilepsy of whom eight out of the 13 were the focal onset, including two with benign childhood epilepsy with centrotemporal spikes. All eight had complex partial seizures and five out of the eight had experienced secondary generalization. Five children among the 13 had primary generalized epilepsy; two of these five had childhood absence epilepsy, two had generalized tonic–clonic epilepsy and one out of the five had myoclonic epilepsy.

Three out of the 16 children had cryptogenic epilepsy, all focal onset with complex partial seizures and one had secondary generalization.

Discussion

This observational pilot study documented two main findings. First, half of the mothers of children with comorbid ADHD+E themselves met DSM-IV criteria for a diagnosis of ADHD. Second, among these mothers, those with a family history of epilepsy in first- or second-degree relatives (in addition to the index child), were more likely to have a diagnosis of ADHD and demonstrated a higher rate of current ADHD symptoms.

The prevalence of ADHD observed in our group of mothers is much higher than typically observed among mothers of children with uncomplicated ADHD. Faraone and colleagues found that 18% of mothers of children with ADHD met the diagnostic criteria for lifetime ADHD [23]. Similarly, Chronis *et al.* reported a rate of 16.7%, much higher than the 0.9% rate observed in mothers of healthy controls [24]. Furthermore, Sprich and colleagues reported that 18% of biological parents of children with ADHD suffered from the disorder themselves, compared with 6% of adoptive parents and 3% of parents of healthy controls [25].

There is a significant literature documenting elevated rates of psychopathology in family members of children with epilepsy, with or without comorbid psychopathology. One-third of mothers of children with epilepsy scored above clinical cut-offs on depression measures, such as the Center for Epidemiologic Studies Depression Scale [26,27]. Whether these elevated rates of depression are a consequence of caring for a child with a medical illness or due to a shared genetic or environmental cause of depression and epilepsy is unclear. In addition,

these findings have not been consistently replicated [28].

To the author's knowledge, no prior studies have specifically examined the rates of ADHD in relatives of children with epilepsy. The most relevant study to date is one by Hoare, who found that mothers of children with chronic epilepsy and with behavior problems had higher levels of psychopathology than mothers whose children with epilepsy did not have behavior problems [29]. Moreover, the parents of children without comorbid behavior problems did not differ significantly from healthy controls in terms of their own psychopathology [29]. This study is particularly interesting in that it suggests that epilepsy comorbid with a behavioral disorder may follow a route that is more heritable than epilepsy or behavior problems alone. Another study by Bennett-Back and colleagues examined 40 children with epilepsy and found that 28 (70%) of them manifested ADHD, while in their sibling control group (n = 12), two siblings (16.7%) manifested ADHD [30]. While the 16.7% (or two out of 12) of the sibling control group is higher than the 3–5% in the general population, the numbers are so low that the proportion is potentially unstable. This study also excluded children with epilepsy whose ADHD preceded their epilepsy.

Although the inattentive subtype of ADHD is the most common in children with epilepsy, the Fam^+ mothers reported more inattention symptoms than Fam^- mothers, but the difference did not achieve an accepted level of statistical significance. Whether this is due to the small sample size in this pilot study or another reason should be addressed in future studies.

This pilot study had several limitations, the most significant being the small sample size, particularly for Fam^+ mothers. This very small sample size makes the results potentially unstable. Nonetheless, it is encouraging to be able to demonstrate a result that is entirely consistent with the abovementioned hypothesis, despite the sample size and heterogeneity of epilepsy diagnoses. In addition, because the mothers were recruited from a randomized control-treatment trial, the ADHD in the children may well have been more symptomatic on average than that seen in the general population of children with comorbid ADHD+E, thus increasing the chances for detecting a familial component. The mothers who declined to participate in this study may also be different to the ones who participated; unfortunately, information regarding the decliners was not collected owing to ethical standards and Institutional Review Board regulations. Finally, restricting the analysis to mothers and not other family members is a limitation, particularly if inheritance patterns differ between mothers and fathers.

This study suggests that epilepsy and comorbid ADHD may share a common heritable route. The observed rate of ADHD among mothers of children with ADHD+E was much higher compared with that observed in mothers of children with ADHD only, and Fam^+ mothers appeared to be especially vulnerable. Although these findings must be considered preliminary, given the study's limitations, they indicate that the question merits a more comprehensive and rigorous investigation enrolling a larger number of participants.

Conclusion

The prevalence of ADHD in mothers of children with ADHD+E is elevated in this pilot study, suggesting that ADHD symptoms in children with epilepsy and their mothers reflect shared familial genetic or environmental risks, potentially resulting in a higher prevalence of both disorders among family members. Larger controlled studies are warranted.

Future perspective

In the next 5–10 years, the field will further understand how genetic defects, some single and others, such as copy number variants that can disrupt several genes, interact with patient's other genes and his or her environment. The field will start to appreciate how these interacting factors vary the penetrance of genetic abnormalities to give rise to phenotypes that cross ICD-9 and DSM categories. Epilepsy increases the risk for a host of psychiatric disorders and many psychiatric disorders, including ADHD, increase the risk for epilepsy. Thus, psychiatric and neurodevelopmental disorders associated with epilepsy will provide a rich source of insight into the genes and mechanisms behind observations, such as the one described in this paper where shared genetic substrates seem to give risk to ADHD+E in one group of family members and ADHD either alone or in combination with other neurodevelopmental disorders in another set of family members. In the simplest and best understood cases, knowledge of the basic mechanisms behind these associations will be translated into therapies that will improve both neuropsychological functioning and ADHD symptoms in these patients.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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