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Speed and Complexity Characterize Attention Problems in Children with Localization-Related Epilepsy

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Summary

Objective—Children with epilepsy (EPI) have a higher rate of ADHD (28–70%) than typically developing (TD) children (5–10%); however, attention is multidimensional. Thus, we aimed to characterize the profile of attention difficulties in children with epilepsy.

Methods—Seventy-five children with localization-related epilepsy ages 6–16 and 75 age-matched controls were evaluated using multimodal, multidimensional measures of attention including direct performance and parent ratings of attention as well as intelligence testing. We assessed group differences across attention measures, determined if parent rating predicted performance on attention measures, and examined if epilepsy characteristics were associated with attention skills.

Results—The EPI group performed worse than the TD group on timed and complex attention aspects of attention ($p<.05$), while performance on simple visual and simple auditory attention tasks was comparable. Children with EPI were 12 times as likely as TD children to have clinically elevated symptoms of inattention as rated by parents, but ratings were a weak predictor of attention performance. Earlier age of onset was associated with slower motor speed ($p<.01$), but no other epilepsy-related clinical characteristics were associated with attention skills.

Significance—This study clarifies the nature of the attention problems in pediatric epilepsy, which may be under recognized. Children with EPI had difficulty with complex attention and

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Supporting Information. Description of subtest procedures for the Test of Everyday Attention for Children (TEA-Ch). Details of anti-epileptic medications for monotherapy and polytherapy patients.

rapid response, not simple attention. As such, they may not exhibit difficulty until later in primary school when demands increase. Parent report with standard ADHD screening tools may underdetect these higher order attention difficulties. Thus, monitoring through direct neuropsychological performance is recommended.

Keywords

cognition; comorbidities; pediatric; ADHD

INTRODUCTION

In the general population, Attention Deficit/Hyperactivity Disorder (ADHD) occurs in approximately 5–10% of children.[1,2,3] In the pediatric epilepsy population, however, the prevalence of ADHD is much higher, ranging from 28–70%.[4,5,6,7,8] Most studies have shown that the Inattentive subtype of ADHD (ADHD-I) is more common in children with epilepsy, whereas the Combined subtype of ADHD (ADHD-C) is more common in developmental ADHD.[6,7,8,9] There are mixed findings about the association between attention skills in children with epilepsy and epilepsy-related clinical characteristics such as number of anti-epileptic drugs (AEDs), location of seizure focus, epilepsy duration, seizure frequency, and age of habitual seizure onset.[7,8,10,11,12]

The nature of attention difficulties in children with epilepsy has not been fully characterized, yet the diagnostic difference of less impulsivity and hyperactivity suggests that children with co-morbid epilepsy and ADHD may have a unique cognitive profile. Most previous studies are limited by how they assessed attention—either by parent/teacher reports or with a continuous performance task.[6,7,10,13,14,15,16,17] This study addresses a gap in the literature by characterizing attention problems in children with epilepsy with a measure that assesses several components of attention. The Test of Everyday Attention for Children (TEA-Ch) was developed to measure functionally separable attentional systems in children using visual and auditory sensory stimuli in both simple and complex attention tasks (Table 1)[18] and has been used in several studies of children with ADHD.[19,20,21] Two pediatric epilepsy studies using the TEA-Ch found that children with epilepsy performed worse than controls; however, the sample sizes were small (n=17 and 7) and the authors did not delve into the pattern of attention impairments.[22,23]

The aim of this study is to characterize attentional deficits in a large cohort of children with localization related epilepsy (EPI) compared to typically developing (TD) healthy volunteers by using a multimodal, multidimensional approach. We hypothesized that children with epilepsy will have greater difficulties with attention on direct testing and parent-report measures. Specifically, we hypothesized that the EPI group will perform worse than controls across attention tasks and demonstrate significant deficits for tasks with auditory and speeded demands.[9,10,12,17] We also hypothesized that parent report of inattentive symptoms will be higher in children with EPI than TD children and predict performance on direct measures of attention. We expected that more AEDs, frontal foci, longer epilepsy duration, greater seizure frequency, and younger age of onset will be associated with worse performance and higher parent ratings of inattention.

METHODS

Participants

One hundred and fifty children ages 6–15 were included in the study if they had completed the TEA-Ch and intellectual testing (Table 2). Seventy-five children with a confirmed diagnosis of localization-related epilepsy were age-matched to 75 typically developing children. Participants were recruited through multiple clinical research protocols with primary aims different from this study but included common measures. Children were excluded if IQ<70 to rule out global impairment as the reason for attention problems.

Characteristics of children with epilepsy are detailed in Table 3. Seizure type was determined by a neurologist who made the diagnosis of focal epilepsy with alteration of consciousness from clinical features, neurologic examination, (video-) EEG, and/or high resolution epilepsy protocol MRI. Children with primary generalized epilepsy were excluded; however, seven (9.3%) have secondarily generalized seizures. Most children with epilepsy had left-hemisphere localized seizures due to a recruiting bias of the primary aims of several of our clinical research protocols that examine language reorganization and have left-sided seizure focus as an inclusion criterion.[24,25,26,27] Most children with epilepsy had normal MRI findings as children. Children were excluded if large (i.e., multi-lobar) abnormalities, tumors, or vascular etiologies including stroke were evident on MRI. However, 19 children (25.3%) with smaller lesions including mesial temporal sclerosis, small focal cortical dysplasias, or nonspecific increased signal changes were included in the study. Number of anti-epileptic drugs ranged from none to four; specific drugs are included in supporting information. Mean age of habitual seizure onset was 6.27 years old (SD=3.17). Seven children with epilepsy had been previously diagnosed with ADHD, three of whom were taking stimulant medication at the time of testing. In the EPI group, one child had a history of anxiety and one had a history of depression. TD children were excluded if there was a known history of a medical disorder or CNS injury (i.e., diabetes, infection, head injury, etc.), learning disabilities, ADHD, or a significant ongoing medical condition.

The study was approved by Children’s National Medical Center Institutional Review Board, with informed consent provided by the parents, and assent provided by all children.

Measures

Direct Measure of Attention—The TEA-Ch[28] is a standardized clinical battery designed to assess attention across various component skills in children. All nine subtests of the TEA-Ch could not be administered due to practical time constraints given that children were participating as part of a larger clinical research protocol that assessed several cognitive domains. We used four subtests to assess simple visual attention (Sky Search), simple auditory attention (Score), complex auditory attention (Score Dual Task (Score DT)), and multimodal (auditory and visual) complex attention (Sky Search Dual Task (Sky Search DT)). We selected these four subtests of the TEA-Ch to be able to look first at a basic level skill, then examine the complex versions where the same basic skills are then combined. We also wanted to include some tasks that had no graphomotor demands given that motor skills can be affected by medications. We included the scaled scores for the accuracy and timed components from the Sky Search subtest. A single scaled score is generated from the other three subtests. Detailed descriptions of subtests are provided in Table 1 and Supporting Information.

Parent Rating of Attention—The ADHD Rating Scale-IV[29] is a standardized parent questionnaire that corresponds to the 18 symptoms for ADHD from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), including nine symptoms of inattention and nine symptoms of hyperactivity/impulsivity. Parents rate symptom frequency over the past 6 months on a four point Likert scale ranging from "Never" to "Very Often." Normative T-scores from the Inattention and Hyperactive/Impulsive subscales are generated. In addition, symptoms rated as "Often" or "Very Often" are considered clinically significant. T-scores and the raw number of clinically significant symptoms (e.g., rated 2 or 3) for Inattention and Hyperactivity/Impulsivity subscales were used in statistical analyses.

Intelligence Testing—The Wechsler Abbreviated Scale of Intelligence (WASI)[30] is a brief assessment battery of intelligence for ages 6–89. It consists of four subtests: two assessing verbal skills and two assessing nonverbal reasoning abilities. These four subtests yield a verbal intelligence quotient (VIQ), a performance intelligence quotient (PIQ), and a full-scale intelligence quotient (FSIQ). We examined VIQ and PIQ independently in our analyses given that one PIQ subtest is timed and may be influenced by motor speed, which we hypothesized may be lower in children with epilepsy.

Data Analysis

Statistical analyses were conducted using SPSS version 21.0 using the appropriate parametric or nonparametric analysis corrected for multiple comparisons. Sample characteristics (*e.g.*, age, gender) and their potential effect on the primary hypotheses of interest were assessed with descriptive and correlational analyses. The primary analyses (multivariate analyses of variance; MANOVA) assessed group (EPI/TD) differences on 1) direct measures and 2) parent ratings of attention. Post-hoc analysis determined specifically which subtests were different. Linear regression was conducted to determine if parent-rating scores predicted performance on direct measures of attention. Additional analyses focused on the impact of epilepsy characteristics on direct and parent reported attention. Characteristics of interest included: a) number of antiepileptic medications (≤ 1 and ≥ 2), b) seizure focus (frontal, temporal, frontotemporal), c) duration of epilepsy (new onset (< 3 years) and chronic (>3 years)), d) seizure frequency in previous 6 months (none, weekly, monthly), and e) age of habitual onset. Categorical distinctions for some linear variables were selected based on a restricted or skewed range of values, clinical relevance, and/or to distribute cell counts to optimize statistical analyses (Table 3). To reduce multiple comparisons, epilepsy characteristics and linear regression of parent-report were only conducted for the attention variables that were found to differ between the EPI and TD group. That number of variables was then used to set a Bonferroni corrected threshold ($.05/5 = p<.01$).

RESULTS

Demographics and IQ

EPI and TD groups were similar in terms of age and gender, thus these factors were not included in further analyses. Although IQ for both groups fell in the Average range, the TD group had significantly higher VIQ and PIQ than the EPI group (Table 2). VIQ was included as a covariate in the MANOVA to account for group differences in IQ while preserving differences related to motor speed that also shares variance with PIQ.

Attention

Direct Measure—Overall, the EPI group performed worse than the TD group on the TEA-Ch subtests ($F_{5,143}$= 3.56, p = .005; Figure 1 and Table 4). Post-hoc analysis demonstrated that the EPI group was slower than the TD group at target identification during the simple visual task ($F_{1,147}$= 5.82, p = .017, d = .51). The EPI group also performed worse on both subtests of complex attention: Sky Search DT ($F_{1,147}$= 11.09, p = .001, d = .64) and Score DT ($F_{1,147}$= 6.15, p = .016, d = .56). A majority (64% Score DT and 68% Sky Search DT) of the EPI group performed at least a standard deviation below the normative average. In contrast, the EPI group demonstrated similar accuracy to the TD group on the simple attention tasks (Sky Search: p = .36; Score p = .20), with both groups performing in the average range.

Parent Rating—Parents of the EPI group were 12 ½ times more likely than parents of the TD group to report clinically elevated levels (≥ 6 symptoms) of inattention (χ^2 = 11.81, p = .001, OR = 12.66); no group difference was found for symptoms of hyperactivity (χ^2 = 1.03, p = .310). Twenty-four percent of the EPI group met DSM-IV symptom criteria for an ADHD diagnosis based on parent ratings (Table 5), compared to 4% of controls. Linear regressions revealed that parent ratings of inattention predicted two aspects of attention performance: speed and complex auditory attention, accounting for 7% and 10% of the variance respectively (Sky Search Time per Target: F (1,136) = 10.19, p = 0.002; Score! DT: F (1,136) = 14.86, p < 0.001). There was a trend for parent ratings to predict complex visual and auditory attention, predicting 3% of the variance (Sky Search DT: F (1,136) = 3.40, p = 0.07).

Epilepsy-related Clinical Characteristics—Earlier age of onset was associated with slower motor speed (r = .32, p = .005). In addition, parents of children experiencing weekly seizures reported more symptoms of hyperactivity than parents of children with no seizures in the previous 6 months (U = 82.50, p = .005, d = .69). Although not significant with the Bonferroni-corrected threshold, there was a large effect size[31] for number of clinical symptoms of attention for parents of children with chronic epilepsy compared to recent-onset epilepsy (t_{66} = −2.27, p = .03, d = .56). Neither number of AEDs nor the location of the epileptogenic foci was related to direct or parent measures of attention (p's>.60).

DISCUSSION

We found that children with localization-related epilepsy performed worse than TD children on complex and timed attention tasks, with a majority of the EPI group performing below average on the complex attention tasks. Moreover, this was not due to IQ differences, which were accounted for statistically. Notably, the EPI group performed comparably to the TD group on simple visual and auditory tasks. Parents of children with EPI endorsed more DSM-IV symptoms of ADHD than parents of the TD group, with 24% of the EPI group meeting criteria for an attention disorder. Parent ratings weakly predicted direct performance on attention measures, indicating the need for both methods of assessment. Attention difficulties were not related to specific epilepsy-related clinical characteristics but slow motor speed was related to earlier age of onset and increased hyperactivity was associated with more frequent seizures. Our elucidation of the nature of attention problems in children with localization-related epilepsy has important implications for understanding the clinical course of the cognitive comorbidities of epilepsy. Identifying the specific attentional weaknesses common to children with epilepsy will inform diagnostic and treatment decisions. This information is particularly important given the association between ADHD and reduced school performance and academic attainment.[32]

Diagnostic Implications

A child with epilepsy who has the attention profile found in our study may not necessarily exhibit functional impairments until complexity or demands for speed increase. Typically these increased demands are required later in a child's education when he or she is asked to attend to two tasks simultaneously (*e.g.*, listening to the teacher while taking notes). Therefore, a child with epilepsy may not present to a medical provider until later in childhood because their age-appropriate simple attentional skills buoy them during the early years. This clinical presentation may lead to diagnostic uncertainty or even under diagnosis. One issue is that the DSM inattentive symptoms reflect simple inattention (*e.g.*, failure to give close attention to details, not listening when spoken to directly, difficulty with sustained attention) rather than complex demands for dividing or shifting attention. Another issue is the required presence of several symptoms prior to age 7 in order to meet the DSM-IV criteria. These issues potentially explain the large range of ADHD comorbidity rates in epilepsy (28–70%) in the existing literature.[4,5,6,7,8] Recent DSM-5 changes that increase the onset age from 7 to 12 may help to clarify rates of ADHD comorbidity in children with epilepsy.

The children with epilepsy in our study have generally well-controlled localization related epilepsy, average IQ, and average simple attention. They are at risk because problems with complex attention may be missed and thus go undiagnosed and untreated. This is reflected in our findings as 17 children with epilepsy met ADHD criteria via parent-reported symptoms, but only 4 had been previously diagnosed with ADHD. Our sample is similar to previous studies in that the inattentive subtype of ADHD was the most common presentation. Moreover, the frequency of ADHD—based on parent report—in our pediatric epilepsy sample (24%) is similar to the frequency of ADHD in epilepsy seen in a large (n=284,419) pediatric epidemiological study (28%).[4] The rate of impairment was strikingly higher (64–

68%) on direct measures of complex attention; however, indicating that clinicians should recommend neuropsychological evaluation in pediatric epilepsy even if parent reported symptoms are low, and other information indicates declining performance (e.g., grades, test performance).

Treatment Implications

Medications have been shown to improve symptoms of ADHD including stimulant (methylphenidate (MPH) and amphetamine) and non-stimulant medications (atomoxetine, guanfacine, and clonidine). While some concerns remain, the majority of recent studies have demonstrated that MPH does not increase seizure frequency or change EEG patterns in children with well-controlled epilepsy.[33,34,35,36,37] Furthermore, MPH reduces symptoms of inattention and hyperactivity[34,35,37] and leads to improved performance on a computerized CPT in children with epilepsy.[36] In developmental ADHD, MPH has demonstrated significant improvement effects on motor and speeded task performance, which could be helpful for children with comorbid epilepsy and ADHD. The positive impact of stimulants is more equivocal with respect to other higher order cognitive skills such as complex attention, working memory, or academic achievement. While there is evidence that stimulants improve academics[38,39] and complex attention/working memory[40] others suggest that the effects are modest on academics[41] or that there is not improvement in complex attention (dual-task) performance in children with ADHD.[20,42] Thus, having a child's profile of attentional difficulties may be informative in understanding and predicting response/nonresponse to stimulants.

Implications Related to Epilepsy

Epilepsy is a heterogeneous medical condition but a majority of individuals have average IQ.[43] We were able to control for some factors by excluding patients with generalized epilepsy, large structural abnormalities, or IQ<70. Within our group, problems with complex attention problems were pervasive regardless of age of habitual seizure onset, seizure frequency, number of medications, or seizure location. However, the children with early age of habitual seizure onset demonstrated slower motor speed. Perhaps the motor system is vulnerable to early neurological disruption related to seizures or treatments. We also found that EPI children with hyperactive symptoms had greater seizure frequency (weekly), which suggests that greater disease burden is associated with a more severe ADHD presentation.

Our results expand the interpretation of previous studies in pediatric epilepsy that have largely used a computerized continuous performance task (CPT) to assess attention. The CPT requires children to quickly press a button for visual targets while ignoring non-target items. On this type of task children with epilepsy have difficulty with sustained attention due to omission errors.[10,15,17] In light of our results, we propose that the quick motor response required for the CPT may be the specific liability rather than the demand for sustained simple attention. The CPT is often used, particularly in drug studies, due to its ease of administration[44]; however, it may not adequately assess attentional impairments in children with epilepsy. Our findings suggest that using measures that distinguish among several components of attention (*e.g.*, different modalities and levels of complexity) is important to accurately identify the core difficulties of children with localization-related epilepsy.

Limitations

Future studies could further investigate clinical characteristics of epilepsy not evaluated here such as other epilepsy types (*e.g.*, generalized epilepsy, epilepsy syndromes), specific AED effects, or specific MRI findings. A second limitation is that we did not have an ADHD-only group to better isolate the unique effects of seizures on attentional functioning. Another potential limitation is that three children in our EPI sample were taking a stimulant at the time of testing; however as noted above, a prior study indicated that MPH would not have affected TEA-Ch performance on the dual tasks but could have bolstered motor task performance. Nonetheless, if MPH had neuroenhancing effects that produced better performance across TEA-Ch tasks for these participants, it would only have made it more difficult for our group differences to reach statistical significance.

Conclusions

Children with localization-related epilepsy and average IQ demonstrate difficulty with attention as complexity and time demands increase, while they maintain their ability to attend to simple visual and auditory stimuli. Poor attention was not associated with seizure frequency, number of antiepileptic medications, age of onset, or location of seizure focus. This translates to diagnostic and treatment implications for pediatricians who may assume the majority of their medical care. Diagnostically, 24% of children with epilepsy meet criteria for an attention disorder based on parent ratings, but a higher prevalence of difficulties (64–68%) is evident on direct testing that distinguishes between timed/untimed and simple/complex attention demands. Treatment decisions and response are better informed with this more comprehensive view of the attention difficulties in pediatric epilepsy. Future studies that assess attention profiles in order to predict response to stimulant treatment and specify the developmental timing of these attention problems will be informative.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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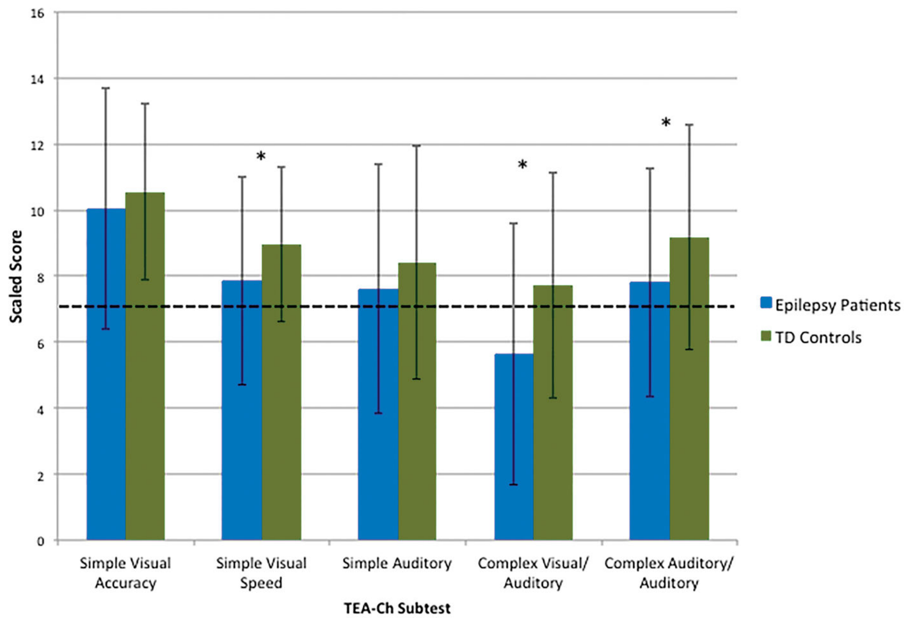

Figure 1.

Performance differences across subtests from the Test of Everyday Attention for Children (TEA-Ch). Dotted line indicates performance 1 SD below average. *= p< .01.

Table 1

Description of Test of Everyday Attention for Children (TEA-Ch) subtests

Subtest	Level	Modality	Attentional Skill(s)	Skill Definition
Sky Search	Simple	Visual	Selective Attention	The capacity to select target information from an array of distractors.
Score!	Simple	Auditory	Sustained Attention	The capacity to maintain focus and alertness over time.
Sky Search DT	Complex	Visual & Auditory	Divided Attention Selective Attention Sustained Attention	(Div. Attn) The capacity to change attentive focus in a flexible and adaptive manner; the ability to attend to more than one stimulus at the same time.
Score! DT	Complex	Auditory	Divided Attention Selective Attention Sustained Attention	

Table 2

Demographic, IQ, and parent reported symptoms of ADHD.

	Patients (n=75)			Controls (n=75)			p value
Gender (% Male)	**56.0**			**44.0**			**.142**
	M(SD)	**Range**	**CI 95%**	**M(SD)**	**Range**	**CI 95%**	
Age	10.09 (2.47)	6–15	9.52–10.66	10.13 (2.40)	6–15	9.58–10.58	.927
FSIQ	99 (15)	71–139	95–102	109 (14)	72–139	106–112	<0.001
VIQ	100 (16)	71–141	97–104	109 (16)	74–145	105–113	<0.001
PIQ	97 (15)	70–142	94–100	107 (13)	75–133	104–110	<0.001

Data is presented as mean(standard deviation), range, and 95% confidence interval.

Table 3

Epilepsy characteristics of patient population.

	Count (Percentage) (n=75)
Chronicity	
Diagnosis 0–3 yrs ago	32 (43%)
Diagnosis >3 yrs ago	43 (57%)
Hemisphere of Seizure Focus	
Left Hemisphere	54 (72%)
Right Hemisphere	17 (22%)
Bilateral	3 (4%)
Undetermined	1 (1%)
Lobe of Seizure Focus	
Temporal	19 (25%)
Frontal	13 (17%)
Fronto-temporal	13 (17%)
Other	30 (40%)
Undetermined	*21 (28%)*
Parietal	*2 (3%)*
Occipital	*2 (3%)*
Frontal-Parietal	*1 (1%)*
Temporal-Parietal	*3 (4%)*
Temporal-Occipital	*1(1%)*
Number of Current AEDs	
0 or 1	44 (58%)
0	*6 (8%)*
1	*38 (50%)*
2 or more	31 (41%)
2	*19 (25%)*
3	*6 (8%)*
4	*6 (8%)*
Seizure Freq. Previous 6 Mo.	
Weekly	18 (24%)
Monthly	23 (31%)
Occasional*	3 (4%)
None	23 (31%)
Missing	8 (10%)

Data are presented as frequency (percentage) unless otherwise noted.

* *Occasional* denotes 1–5 seizures in the previous 6 months.

Table 4

EPI (n=75) and TD (n=75) performances on subtests of attention.

	Group	M (SD)	CI 95%	p value
Sky Search: Accuracy	EPI	10.04 (3.65)	9.30 – 10.78	.362
	TD	10.55 (2.76)	9.81 – 11.29	
Sky Search: Time per Target	EPI	7.85 (3.14)	7.21 – 8.48	.017
	TD	8.96 (2.33)	8.32 – 9.59	
Score!	EPI	7.61 (3.77)	6.77 – 8.45	.200
	TD	8.42 (3.54)	7.58 – 9.26	
Sky Search DT	EPI	5.65 (3.97)	4.79 – 6.50	.001
	TD	7.72 (3.43)	6.87 – 8.58	
Score! DT	EPI	7.79 (3.46)	7.03 – 8.56	.016
	TD	9.18 (3.40)	8.41 – 9.94	

Data are presented as mean (M), standard deviation (SD), and 95% confidence interval (CI).

Table 5

Parent reported ADHD symptoms.

	Patients (n=68)	Controls (n=75)
>5 ADHD-I symptoms	19%	1%
>5 ADHD-HI symptoms	1%	0%
>5 ADHD-I symptoms and >5 ADHD-HI symptoms	4%	3%
TOTAL	24%	4%

ADHD percentages represent the frequency of those who meet DSM-IV criteria for ADHD (6+ symptoms) based on parent rating of inattentive (ADHD-I) and hyperactive-impulsive (HI) symptoms on the DuPaul rating scale.