FULL-LENGTH ORIGINAL RESEARCH

ADHD in childhood epilepsy: Clinical determinants of severity and of the response to methylphenidate

[1,2]Sylvain Rheims, [2,3]Vania Herbillon, [4]Nathalie Villeneuve, [5]Stéphane Auvin, [6]Silvia Napuri, [7]Claude Cances, [8]Patrick Berquin, [9]Pierre Castelneau, [10]Sylvie Nguyen The Tich, [11]Frédéric Villega, [12]Hervé Isnard, [13]Rima Nabbout, [14]Ségolène Gaillard, [15]Catherine Mercier, [14]Behrouz Kassai, [2,3]Alexis Arzimanoglou, and *the investigators of the Paediatric Epilepsy REsearch NEtwork (PERENE)

Epilepsia, 57(7):1069–1077, 2016
doi: 10.1111/epi.13420

Sylvain Rheims is assistant professor of neurology at Lyon's University Hospital.

Summary

Objective: **Attention-deficit/hyperactivity disorder (ADHD) is commonly observed in children with epilepsy. However, factors associated with the development of ADHD and which might help to guide its therapeutic management, remain an issue of debate.**

Methods: **We conducted a multicenter prospective observational study that included children, aged 6–16 years, with both epilepsy and ADHD according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. After inclusion, patients entered a 12–16 week follow-up period during which they were either treated with methylphenidate or they did not receive specific ADHD treatment. ADHD was evaluated with the ADHD Rating Scale-IV.**

Results: **One hundred sixty-seven patients were included, of which 91 were seizure-free during the preinclusion baseline period. At inclusion, the ADHD Rating Scale-IV total score was 30.4 ± (standard deviation) 9.2, the inattentive subscore was 17.3 ± 4.4, and the hyperactive subscore was 13.2 ± 6.6. We did not detect any difference of ADHD Rating Scale-IV scores across patients' age or gender, age at epilepsy onset, epilepsy syndrome, seizure frequency, or number of ongoing antiepileptic drugs. Methylphenidate was initiated in 61 patients, including 55 in whom a follow-up evaluation was available. At the last follow-up, 41 patients (75%) treated with methylphenidate and 39 (42%) of those who did not received ADHD therapy demonstrated ≥25% decrease of ADHD Rating Scale-IV total score ($p < 0.001$). Response to methylphenidate was greater in girls but was not influenced by any epilepsy-related variables.**

Significance: **We did not detect any epilepsy-related factor associated with the severity of ADHD. Twenty-five percent of patients did not respond to methylphenidate. A better understanding of the pathologic process that underlies ADHD development in childhood epilepsy might be required to improve therapeutic strategies.**

Accepted April 25, 2016; Early View publication May 29, 2016.

[1]Department of Functional Neurology and Epileptology and Epilepsy Institute (IDEE), Hospices Civils de Lyon and Lyon 1 University, Lyon, France; [2]Lyon's Neuroscience Research Center, INSERM U1028/CNRS UMR 5292, Lyon, France; [3]Epilepsy, Sleep and Pediatric Neurophysiology Department, Hospices Civils de Lyon, Lyon, France; [4]Department of Pediatric Neurology, APHM, Marseille, France; [5]AP-HP, Department of Pediatric Neurology, Robert Debré Hospital, Paris, France; [6]Department of Pediatric Neurology, Rennes University Hospital, Rennes, France; [7]Department of Pediatric Neurology, Children Hospital, Toulouse, France; [8]Department of Pediatric Neurology, INSERM U1105 CURS, Amiens, France; [9]Department of Pediatric Neurology, University Hospital of Tours, Tours, France; [10]Department of Pediatric Neurology, University Hospital of Lille, Lille, France; [11]Department of Pediatric Neurology, University Hospital of Bordeaux, Bordeaux, France; [12]Lyon's University Hospital, Lyon, France; [13]Pediatric Neurology Department, Reference Center for Rare Epilepsies, Necker Hospital, Paris, France; [14]Department of Clinical Pharmacology, EPICIME-CIC 1407 Inserm, Hospices Civils de Lyon, Lyon, France; and [15]Department of Biostatistics, Hospices Civils de Lyon, Lyon, France

Address correspondence to Sylvain Rheims, Department of Functional Neurology and Epileptology, 59 Boulevard Pinel, 69003 Lyon, France. E-mail: sylvain.rheims@chu-lyon.fr

*The names of investigators available in Appendix S1.

KEY WORDS: Epilepsy, Attention-deficit/hyperactivity disorder, Methylphenidate.

Key Points

- Because of its impact on quality of life and cognition, comorbid ADHD represents a key aspect of the management of children with epilepsy
- ADHD symptoms are not associated with the underlying epilepsy syndrome, the severity of epilepsy, and/or the ongoing antiepileptic drugs
- Methylphenidate resulted in a clinically significant decrease of ADHD symptoms in 75% of patients
- Response to methylphenidate was greater in girls but was not influenced by any epilepsy-related variables
- Methylphenidate was not associated with increased risk of seizure relapse
- Because of the limitations related to its observational design, the results of this study will have to be confirmed in a randomized double-blind controlled trial

Attention-deficit/hyperactivity disorder (ADHD) is observed in about one third of children with epilepsy and appears as one of the crucial elements of quality of life for them.[1] ADHD significantly contributes to cognitive difficulties,[2] and its management has thus emerged as one of the main priorities in these patients.[3] However, factors associated with the development of ADHD and which might help to guide its therapeutic management remain to be determined.

Although ADHD might be observed in up to 70% in children with drug-resistant epilepsy,[4] no formal correlation has been established between the presence of ADHD and the type of epilepsy, the duration of epilepsy, the seizure frequency, the antiepileptic treatments, or the co-occurrence of other psychiatric comorbidities (i.e., mood or anxiety disorders).[2,4,5] Similarly, the clinical determinants of the response to methylphenidate (MPH), the first-line pharmacologic treatment of ADHD with or without epilepsy,[6] remain unknown. Previous studies have shown that treatment with MPH results in clinically significant decrease of ADHD symptoms in 60–80% of children with epilepsy and ADHD.[7–13] Although it has been suggested that efficacy of MPH might be lower in patients with idiopathic generalized epilepsy or in patients with predominantly inattentive subtype ADHD,[8] this observation has not been confirmed by others.[7,9] However the sample size of these studies, which ranged from 12 to 33 patients,[7–13] might have been too small to identify factors associated with response to MPH.

To address these issues, we studied the clinical determinants of severity of ADHD symptoms and of response to MPH in a multicenter observational prospective study, into which 167 children with both epilepsy and ADHD were either treated with MPH or did not receive specific ADHD treatment during a 12–16 week follow-up period.

Methods

The study consisted of a prospective observational study fulfilling the STROBE checklist (see Appendix S2). Registration number was NCT01482026.

Study population

Patients were recruited by 10 French pediatric epilepsy departments (see Appendix S1) between November 2011 and September 2014, according to the following inclusion criteria: (1) age ≥6 years and <16 years; (2) patients having epilepsy according to International League Against Epilepsy (ILAE) classification[14] regardless of underlying epilepsy syndrome, seizure frequency, or ongoing antiepileptic drug treatment; (3) diagnosis of ADHD of Inattentive subtype (ADHD-I) or combined Inattentive/Hyperactive-Impulsive subtype (ADHD-C) according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria except for the criterion of onset before age of 7[15]; (4) no ongoing specific ADHD treatment, including methylphenidate and atomoxetine.

ADHD was diagnosed by the treating physician according to the DSM-IV criteria. None of the participating centers used the ADHD Rating Scale-IV as a screening tool in all patients with epilepsy. According to previous studies that showed that inattention was the core symptom of ADHD in children with epilepsy,[2,4] patients with ADHD Hyperactive-Impulsive subtype[15] were not included in the study. Patients with a significant intellectual disability based on clinical evaluation or using the Wechsler Intelligence Scale for Children-Fourth Edition (WISC IV, IQ <70) were excluded. Specifically, a clinical evaluation was performed by the treating neuropediatrician. In patients suspected of mental retardation, a full neuropsychological evaluation using the WISC-IV was then performed by a neuropsychologist.

The study has been approved by both the ethics committee (CPP Sud Est II n°2011-042-AM1) and the competent authority (CCTIRS n° 11.530). All patients agreed to participate in the study and their parents/legal guardian provided written informed consent prior to participation in the study.

Study design

Patients were seen at the inclusion visit and after a 12–16 week follow-up period. Baseline clinical features were collected at the inclusion visit, including demographic characteristics (age, gender, and medical history), school difficulties (history of repeated grade), parents' subjective judgment of academic progress (i.e., good, average, or poor) and specific educational program, epilepsy features (type of epilepsy, age at seizure onset, epilepsy duration, ongoing antiepileptic drug treatment, and seizure frequency in the 4 weeks before inclusion as determined by patient and/or parent reports) and characteristics of ADHD (ADHD subtype according to DSM-IV,[15] age at ADHD onset). The type of epilepsy was classified into five groups according to ILAE classification[14]: (1) nonidiopathic focal epilepsy; (2) idiopathic focal epilepsy, including benign epilepsy with centrotemporal spikes and Panayiotopoulos syndrome; (3) childhood absence epilepsy; (4) other genetically determined generalized epilepsies, including juvenile myoclonic epilepsy and epilepsy with grand mal on awaking; and (5) other types of epilepsy. For patients who were seizure-free during the 4-week preceding study entry, investigators were asked to indicate whether epilepsy was controlled or still active. Epilepsy was judged as controlled in patients who achieved a seizure-free period ≥12 months.

According to the inclusion criteria, none of the included patients received specific ADHD treatment at study entry. The inclusion visit corresponded to an outpatient visit planned in the habitual follow-up of the patient during which the treating physician decided, after discussion with the patients' parents, either to introduce MPH or to follow-up the patient without specific pharmacologic intervention for ADHD. For patients in whom MPH was initiated, titration and target dose were managed according to French guidelines,[16] with a dosage of 0.3–1.0 mg per kilo either two to three times per day (short-acting MPH) or once per day (slow-acting MPH).

Baseline level and evolution of ADHD symptoms were evaluated with the ADHD Rating Scale-IV, which was scored at study inclusion and at the end of the follow-up. The latter quantifies each of the 18 symptoms of ADHD on a scale of 0–3, with a maximum score of 54 points. Nine of the 18 items score for inattention, whereas the nine others assess hyperactivity with a maximum of 27 points each. The ADHD Rating Scale-IV is correlated with other measures of ADHD symptoms, including the Clinical Global Impressions-ADHD-Severity.[17,18] The patients who were rated mildly ill demonstrated in average a total score of the ADHD Rating scale-IV >20, those moderately ill a total score of the ADHD Rating Scale-IV >30, those markedly ill a total score of the ADHD Rating Scale-IV >35, and those severely ill a total score of the ADHD Rating Scale-IV >40.[18] The discriminative value of the scale was validated in patients without epilepsy,[17] and its use as outcome measurement in studies investigating ADHD treatments has been recommended by the European Medicines Agency.[19] ADHD Rating Scale-IV was thus used as the primary endpoint in several clinical trials,[20–22] including studies of MPH in children with epilepsy and ADHD.[8] In these trials, the level of significant clinical response was set at a 25% reduction in the total score.[20,23]

AEDs remained unchanged throughout the study and patients and/or their parents completed daily record cards on which they logged the number, description, and date of each seizure.

Statistical analyses

Clinical determinants of ADHD severity at baseline

The association between the total score or the two sub-scores of the ADHD Rating Scale-IV and patients' baseline clinical characteristics (i.e., patients' gender, epilepsy syndrome, active epilepsy, number of ongoing AEDs, history of repeating grades, and parental estimation of school performances) was assessed with chi-square or Student's *t*-test, where appropriate. Adjustments for multiple comparisons were made using the Bonferroni method.

Clinical determinants of response to MPH

The differences between the MPH group and the control group were compared regarding baseline clinical characteristics (i.e., patients' age, patients' gender, epilepsy syndrome, age at epilepsy onset, active epilepsy, number of ongoing AEDs, history of repeating grades, parental estimation of school performances, and type of ADHD), baseline total score and subscores of the ADHD Rating Scale-IV and changes in the ADHD Rating Scale-IV total score and subscores between baseline visit and follow-up visit, using Fisher exact probability test, chi-square, or Mann-Whitney *U* tests, where appropriate. For changes in scores, a 0.05 threshold was considered significant. Adjustments for multiple comparisons were made using the Bonferroni method for the other comparisons.

The association between the use of MPH and the difference between the ADHD Rating Scale-IV total score at the end of the follow-up and the baseline score was assessed using a linear regression model after adjustment for baseline ADHD Rating Scale-IV total score. Interactions between response to MPH and baseline clinical characteristics were further assessed using a stepwise approach, where only significant predictors at $p < 0.1$ were kept in the final model.

Similarly, the association between the number of patients who demonstrated ≥25% decrease of ADHD Rating Scale-IV total score at the end of the follow-up in comparison with the baseline score and the use of MPH was assessed using a logistic regression model after adjustment for baseline ADHD Rating Scale-IV total score. Interactions between the response to MPH and baseline clinical characteristics were further assessed using a stepwise approach, where only

significant predictors at $p < 0.1$ were kept in the final model.

Risk of seizure aggravation in patients who received MPH

The MPH group and the control group were compared on the number of patients who were seizure-free during the 4 weeks preceding study entry and for whom the investigator considered that epilepsy was no longer active but who demonstrated seizure recurrence during the follow-up using Fisher's exact probability test. A p-value of <0.05 was considered statistically significant.

Statistical analyses were performed using SPSS version 13.0 software (SPSS Inc., Chicago, IL, U.S.A.).

Results

Baseline clinical characteristics

A total of 168 patients were screened and 167 were included in the study, including 112 boys (67%) and 55 girls (33%), with a mean age ± standard deviation (SD) of 9.6 ± 2.4 years (Table 1). Absence of significant intellectual disability was based on clinical evaluation in 121 patients (72%), whereas 47 (28%) underwent WISC-IV evaluation. In these latter patients, the median verbal and performance IQ scores were 100 (range 59–150) and 90 (range 58–132), respectively.

Epilepsy

Mean age ± SD at epilepsy onset was 5.0 ± 3.3 years (range 0–14 years). The type of epilepsy was unavailable for four children. Among the other 163 children, 50 (31%) had nonidiopathic focal epilepsy, 46 (28%) idiopathic focal epilepsy, 27 (17%) childhood absence epilepsy, 26 (16%) other forms of genetically determined generalized epilepsies, and 14 (9%) unclassified epilepsy. Age at epilepsy onset significantly varied across syndromes ($p < 0.001$ by Kruskall-Wallis test), with an epilepsy onset at younger age in patients with nonidiopathic focal epilepsy (4.3 ± 3.2 years) and unclassified epilepsy (2.5 ± 2.3 years) than in patients with idiopathic focal epilepsy (6.1 ± 2.9 years), childhood absence epilepsy (5.7 ± 1.9), or other forms of genetically determined generalized epilepsy (5.4 ± 4.4 years). Epilepsy was considered controlled by the treating physician at study entry in 91 patients (54%), including 36 in whom antiepileptic drug (AED) treatment was not considered necessary.

Only 35 patients reported seizures during the 4 weeks preceding study inclusion. In these latter, the median number of seizures during this period was 3.0 (range 1–280), with a significant variation across epilepsy syndromes ($p = 0.029$ by Kruskal-Wallis test). The median number of seizures during the 4 weeks preceding study inclusion was thus 2.5 (range 1–80) in children with nonidiopathic focal epilepsy, 1.5 in those with idiopathic focal epilepsy (range 0–4), 80 in those with childhood absence epilepsy (range 50–280), 2.5 in those with other forms of idiopathic generalized epilepsy (range 1–4), and 3 in those with unclassified epilepsy (1–100).

Attention-deficit/hyperactivity disorder

According to DSM-IV classification, 68 children (42.5%) had ADHD-I and 92 (57.5%) had ADHD-C. Mean age at onset of ADHD symptoms was 5.4 ± 1.9 years (range 2–13 years). In 53 patients (32%), ADHD symptoms preceded epilepsy onset by 2.8 ± 2.4 years in average. In the remaining patients, ADHD symptoms started in average 2.1 ± 1.8 years after the first seizures. Of interest, age at onset of ADHD symptoms and delay between onset of ADHD symptoms and epilepsy significantly varied across epilepsy syndromes ($p = 0.025$ and $p < 0.001$ by Kruskal-Wallis test, respectively). Thus, ADHD symptoms preceded epilepsy onset by a median delay ± interquartile range of 1.08 ± 3.7 years and 0.17 ± 3.6 years in patients with idiopathic focal epilepsy and in those with other forms of genetically determined generalized epilepsies, respectively. In contrast, ADHD symptoms started after epilepsy onset in patients with nonidiopathic focal epilepsy and unclassified epilepsy and, with a median delay ± interquartile range of 1.71 ± 3.6 years and 3.4 ± 2.7 years, respectively. In patients with childhood absence epilepsy, ADHD symptoms started with epilepsy (0.0 ± 1.1 years).

Clinical determinants of severity of ADHD symptoms

At inclusion, the mean ± SD ADHD Rating Scale-IV total score was 30.4 ± 9.2, the inattentive subscore was 17.3 ± 4.4, and the hyperactive subscore was 13.2 ± 6.6. As shown in Table S1, we did not detect any significant difference of ADHD Rating Scale-IV total score or subscores across patient age or gender, age at epilepsy onset, epilepsy syndrome, seizure frequency, or number of ongoing antiepileptic drugs. Results remained similar when analyses were reprocessed in the subgroup of patients who received monotherapy, where the association between ADHD Rating Scale-IV total score and ongoing AEDs could be tested (Table S2). No significant association between school difficulties and ADHD severity was observed.

Pharmacologic intervention for ADHD

MPH was initiated at the inclusion visit in 61 patients (37%), whereas the 106 other patients (63%) were followed up without specific pharmacologic intervention for ADHD. As shown in Table 1, the two groups demonstrated similar baseline characteristics regarding both epilepsy and ADHD, including the ADHD Rating Scale-IV total score and subscores. There was a trend toward greater likelihood of MPH treatment for patients with childhood absence epilepsy, with 59% of them receiving MPH in comparison with 28%, 39%, 19%, and 44% of patients suffering with nonidiopathic focal epilepsy, idiopathic focal epilepsy, other forms of genetically determined generalized epilepsies, and unclassified

Table 1. Patients' baseline clinical characteristics

	All patients	Patients followed without specific pharmacologic intervention for ADHD	Patients in whom MPH was initiated at study entry
Total, n (%)	167	106 (63)	61 (37)
Age, mean ± SD	9.5 ± 2.4	9.5 ± 2.3	9.6 ± 2.4
Gender (boys), n (%)	112 (67)	74 (70)	38 (62)
Epilepsy			
Syndrome, n (%)			
Nonidiopathic focal epilepsy	50 (30)	36 (34)	14 (23)
Idiopathic focal epilepsy	46 (28)	28 (26)	18 (30)
Childhood absence epilepsy	27 (16)	11 (10)	16 (26)
Other forms of genetically determined generalized epilepsies	26 (16)	21 (20)	5 (8)
Others	14 (8)	7 (7)	7 (11)
Unavailable	4 (2)	3 (3)	1 (2)
Age at epilepsy onset, mean ± SD	5.0 ± 3.3	4.8 ± 3.3	5.3 ± 3.2
Active epilepsy, n (%)	76 (46)	48 (45)	28 (46)
Number of ongoing AED, n (%)			
0	36 (22)	21 (20)	15 (25)
1	86 (52)	57 (54)	29 (47)
2	38 (22)	21 (20)	17 (28)
≥3	7 (4)	7 (6)	0
AED, n (%)			
Sodium valproate	69 (41)	46 (43)	23 (38)
Lamotrigine	25 (15)	12 (12)	12 (20)
Ethosuximide	13 (8)	9 (8)	4 (7)
Topiramate	3 (2)	2 (2)	1 (2)
Carbamazepine/oxcarbazepine	27 (16)	19 (18)	8 (13)
Benzodiazepines	19 (11)	14 (13)	5 (8)
Levetiracetam	19 (11)	12 (11)	7 (12)
Other	8 (5)	6 (6)	2 (3)
School performance, n (%)			
History of repeating grades	57 (35)	35 (33)	22 (37)
Parental estimation of school performances			
Very good/good	39 (23)	26 (24)	13 (21)
Intermediate	65 (39)	44 (42)	21 (34)
Insufficient/very insufficient	63 (38)	36 (34)	27 (44)
Specific educational program			
Yes	11 (6)	10 (1)	1 (2)
No	156 (94)	96 (99)	60 (98)
ADHD			
Type, n (%)			
ADHD-I	68 (43)	42 (42)	26 (44)
ADHD-C	92 (57)	59 (58)	33 (56)
Age at ADHD onset, mean ± SD	5.4 ± 1.9	5.3 ± 1.8	5.6 ± 2.1
ADHD Rating Scale-IV, mean ± SD			
Total score	30.4 ± 9.2	29.3 ± 8.4	32.4 ± 10.2
Inattentive subscore	17.3 ± 4.4	16.7 ± 4.1	18.1 ± 4.8
Hyperactivity subscore	13.2 ± 6.6	12.4 ± 6.2	14.3 ± 7.2

epilepsy, respectively. However, this association did not reach statistical significance after correction for multiple comparisons ($p = 0.231$). Patients in whom MPH was initiated demonstrated, on average, a slightly higher ADHD Rating Scale-IV total score than the other group, but the difference did not reach statistical significance after correction for multiple comparisons. Short-acting formulation of MPH was used in eight patients (13%), whereas the 53 remaining patients were treated with slow-acting MPH. The median MPH daily dose was 20 mg (range 5–40).

Patients' follow-up

A total of 160 patients completed the 12–16 week follow-up, including 58 in whom MPH had been initiated at study entry. However, evaluation of the ADHD Rating Scale-IV was not adequately performed at the last follow-up visit in 12 of them, including 4 patients who received MPH. Overall, the evolution of ADHD Rating Scale-IV could therefore be evaluated in 148 patients, including 55 patients in whom MPH had been initiated at study entry and in 93 patients followed up without specific pharmacologic

intervention for ADHD. Among the seven patients who did not complete the study, the study withdrawal was related to MPH adverse events in two and loss to follow-up in five.

Evolution of ADHD symptoms

As shown in Table 2, the evolution of the ADHD Rating Scale-IV total score and subscores significantly differed between patients treated with MPH and those who were followed up without specific pharmacologic intervention for ADHD. At the last follow-up, patients treated with MPH thus demonstrated a mean decrease of ADHD Rating Scale-IV total score of 11.8 ± 11.0 points in comparison with 4.4 ± 8.4 points in the control group ($p < 0.001$). The evolution was similar for inattentive subscore and hyperactive subscore. Overall, 75% of patients treated with MPH demonstrated significant clinical response (i.e., ≥25% decrease of ADHD Rating Scale-IV total score at the end of the follow-up in comparison with the baseline score) in comparison with 42% of those who did not receive any specific pharmacologic intervention for ADHD ($p < 0.001$).

After adjustment on the baseline ADHD Rating Scale-IV total score, the evolution of ADHD Rating Scale-IV total score at the end of the follow-up in comparison with the baseline score was associated with treatment with MPH ($p < 0.001$), younger age at ADHD onset ($p = 0.027$), and diagnostic of idiopathic focal epilepsy ($p = 0.017$). However, no association between significant clinical response and the type of epilepsy was observed. Significant clinical response at the end of the follow-up was thus more frequently observed in girls (odds ratio [OR] 2.48, 95% confidence interval [CI] 1.06–5.79; $p = 0.036$), in patients who were treated with MPH (OR 1.71, 95% CI 1.16–2.53; $p = 0.007$) and was significantly associated with younger age at ADHD onset (OR 1.32, 95% CI 1.06–1.65; $p = 0.012$). In patients who received MPH, there was no association either between the evolution of ADHD Rating Scale-IV total score at the end of the follow-up in comparison with the baseline score and the total daily dose of MPH ($p = 0.178$) or between the latter and significant clinical response (OR 1.07, 95% CI 0.97–1.19; $p = 0.17$).

Tolerability of MPH

Two patients in whom MPH had been initiated at study entry withdrew from the study because of adverse events. Both patients reported symptomatic tachycardia.

Among the patients who were seizure-free at study entry (n = 91), six demonstrated seizure relapse during the follow-up. Specifically, 4 (12.5%) of the 32 patients (12.5%) in whom MPH had been initiated demonstrated seizure recurrence, with a single seizure during the 12–16 week follow-up in one patient, 2 in 2, and 7 in the remaining patient. In contrast, 2 (3.4%) of the 59 patients who did not receive any specific pharmacologic intervention for ADHD reported seizure relapse, with a single seizure in one and four seizures in the other. However, there was no statistically significant difference in the rate of seizure recurrence between the two groups of patients ($p = 0.191$ by Fisher's exact test). Among patients with active epilepsy at study entry, two had clear-cut seizure worsening during the study period, with a threefold increase of the monthly seizure frequency. One of them received MPH, whereas the other did not receive any specific pharmacologic intervention for ADHD.

Discussion

Because of its impact on quality of life and cognitive functioning, comorbid ADHD represents a key aspect of the management of children with epilepsy. Our prospective observational study showed the following: (1) there was no significant association between occurrence and severity of ADHD symptoms, as assessed by the ADHD Rating Scale-IV, and the underlying epilepsy syndrome, the severity of epilepsy, and/or the ongoing antiepileptic drug regimen; (2) MPH resulted in a clinically significant decrease of ADHD symptoms in 75% of patients; and (3) proportion of seizure relapse was not significantly different between patients treated with MPH and those who did not receive any specific pharmacologic intervention for ADHD.

Several tools have been developed to evaluate the severity of ADHD symptoms in children.[24] For clinical

Table 2. Evolution of ADHD symptoms

	Patients followed without specific pharmacologic intervention for ADHD				Patients in whom MPH was initiated at study entry			
	Baseline, mean ± SD	Follow-up, mean ± SD	Evolution, mean ± SD	Number of patients with >25% reduction, n (%)	Baseline, mean ± SD	Follow-up, mean ± SD	Evolution, mean ± SD	Number of patients with >25% reduction, n (%)
Total score	29.3 ± 8.4	24.4 ± 10.3	−4.4 ± 8.4	39 (42)	32.6 ± 9.9	20.8 ± 9.5	−11.8 ± 11.0	41 (75)
Inattentive subscore	16.8 ± 4.1	14.5 ± 5.1	−2.0 ± 4.9	33 (35)	18.1 ± 4.8	11.5 ± 5.8	−6.8 ± 6.3	40 (73)
Hyperactivity subscore	12.5 ± 6.2	10.0 ± 6.2	−2.3 ± 4.5	40 (43)	14.3 ± 7.2	8.4 ± 4.3	−6.0 ± 6.6	37 (67)

investigations of medicinal products for the treatment of ADHD, the European Medicines Agency, however, recommends the use of the Connors' Rating Scales or the ADHD Rating Scale-IV and scales assessed by clinicians.[19] Specifically, the psychometric properties of the ADHD Rating Scale-IV proved to be sufficiently robust for assessing ADHD symptom severity in children without epilepsy.[17] Based on the cohort reported here, we recently confirmed the psychometric validity of the ADHD Rating Scale-IV in children with epilepsy and ADHD, showing a satisfactory reliability of most items, a good dimensional internal consistency, and good responsiveness of the total score and the two subscores.[25]

Our results were in line with previous data that reported, both in newly diagnosed epilepsy[2] and in children with refractory epilepsy,[4] that no formal correlation could be established between the severity of ADHD and the duration of epilepsy, the seizure frequency, or the ongoing antiepileptic drug. However, as reported in childhood absence epilepsy,[26] the risk of developing attention dysfunction might differ across antiepileptic drugs. Because analysis of the association between the severity of ADHD and the AED regimen is difficult to interpret in patients taking two or more AEDs, we limited our analysis to the subgroup of patients receiving monotherapy. This approach, however, reduced the sample size. We therefore could not exclude that this analysis was underpowered to detect significant differences of ADHD Rating Scale-IV total score across AEDs.

Other studies reported that ADHD frequently precedes the occurrence of the first seizure[2,27] and showed that ADHD is a risk factor for the emergence of the seizures.[27,28] In the present cohort, ADHD preceded the occurrence of the first seizure in 32% of patients. Of interest, we observed that the delay between onset of ADHD symptoms and epilepsy significantly varied across epilepsy syndromes. On average, ADHD preceded idiopathic focal epilepsy or other forms of genetically determined generalized epilepsies, whereas epilepsy onset preceded ADHD in nonidiopathic focal epilepsies or unclassified epilepsy. Although these results might have been related partly to the variation of age at epilepsy onset across epilepsy syndromes, they might remain in line with the view that ADHD and epilepsy might share common pathophysiologic mechanisms,[27,29] especially in genetically determined epilepsies.

Therapeutic management of ADHD associated with epilepsy relies on the usual therapy of ADHD,[6] specifically MPH.[30,31] Some studies have specifically evaluated MPH in children with epilepsy.[7–13] These studies, in which sample sizes were limited, ranging from 12 to 33 patients, suggested that the efficacy of MPH is similar to that described in the general population.[32] We also observed that MPH initiation was associated with a significant improvement of ADHD symptoms. It should be noted, however, that, in comparison to the control group and after adjustment on the baseline score, the size of the treatment effect remained small, with an OR for clinically significant response at 1.71 (1.16–2.53). In addition, 25% of patients did not respond to MPH. We did not observe a significant association between the MPH daily dose and the improvement of ADHD symptoms. However, we could not exclude that some patients might have benefited from increasing MPH dose.

Although controversial, some studies have suggested that the use of MPH in children with epilepsy may in some cases be associated with a dose-dependent increase in seizure frequency, raising the seizure frequency up to 60%.[8,33] Furthermore, it was also suggested that receiving MPH may accelerate the occurrence of seizures in nonepileptic children who present epileptiform abnormalities when EEG is carried out systematically before the initiation of treatment.[34] We observed seizure recurrence in 4 (12.5%) of the 32 patients who were seizure-free at study entry and in whom MPH had been initiated. Although a similar worsening was observed in a lower proportion of patients who did not received MPH (3.4%), the difference between the two groups did not reach statistical significance. However, given the sample size in both groups, it remained difficult to draw formal conclusions about the impact of MPH on the risk of seizure recurrence.

Despite its prospective design and large sample size, our study had several limitations that should be taken into account when interpreting the results. Detailed neuropsychological evaluation was not required by the study protocol, and IQ was therefore assessed at the discretion of the treating physician. In all participating centers, full neuropsychological evaluation is usually performed in patients in whom mental retardation is suspected. Those patients with demonstrated IQ <70 were not eligible for inclusion in the study. However, in the absence of systematic evaluation of IQ in all included patients, we could not formally exclude that some of them had IQ <70. Most importantly, the relation between the ADHD severity and the IQ level could not be evaluated. Consequently, we could not rule out that variations of IQ level across patients and/or epilepsy syndrome might have represented a confounding factor. Similarly, EEG data were neither retrieved at baseline nor monitored during the follow-up. To result in informative data, prospective monitoring of EEG would have required a specific design that was beyond the scope of the present study. However, a number of studies have suggested that interictal spikes might negatively impact the cognitive functioning in children with epilepsy.[35] Whether or not severity and/or evolution of ADHD symptoms during the follow-up were associated with the abundance of interictal spikes remained therefore an important open question. Similarly, distinction between seizure-related disturbance of attention and comorbid ADHD might be challenging, especially in patients with childhood absence epilepsy. In these latter, inattention might thus primarily reflect frequent absence seizures rather

than comorbid ADHD. Baseline seizure frequency over the last 3 months was retrospectively assessed at study entry, a design that might have impacted the interpretability both of the relation between ADHD symptoms and the seizure frequency and of evolution of seizure frequency under MPH therapy. Some children might have undergone behavioral interventions. However, this information was not retrieved during the follow-up. The present study includes the largest cohort of children with epilepsy in whom the efficacy of MPH on ADHD symptoms was prospectively evaluated. However, MPH was initiated at the discretion of the treating physician. Although the data retrieved during the study were not sufficiently detailed to allow a formal analysis, noninitiation of MPH might have been related primarily to the reluctance of the physician, the parents, or both to use this drug because of their worry of drug-related adverse events. Furthermore, the follow-up was performed using an open-label design. As a matter of fact, patients in whom MPH was initiated demonstrated, on average, a slightly higher ADHD Rating Scale-IV total score than the other group. Similarly, the distribution of epilepsy syndromes between the two groups of patients was not balanced, with children with childhood absence epilepsy being more likely to be treated with MPH than those suffering from another type of epilepsy. Both the internal validity and the external validity of the results were thus limited and the level of evidence regarding the efficacy of MPH in this population was low. Accordingly, a randomized double-blind controlled trial is required to formally address this issue.

Overall, we did not detect any epilepsy-related factor associated with the severity of ADHD or with a clinically significant response to MPH. Although MPH was efficacious in a majority of patients, one fourth of children did not respond to therapy. Considering the impact of ADHD on quality of life in children with epilepsy, development of alternative and/or complementary therapeutic strategies to MPH is therefore an important issue. However, a better understanding of the pathologic process that underlies ADHD development in childhood epilepsy might be required to unravel specific therapeutic target.

Acknowledgments

The study was funded by the French Ministry of Health (PHRC national 2011-AGPI) and the Pediatric Investigation into Health Products Network (*RIPPS*). We thank Philippe Ryvlin for his help in the design of the study and for his comments on the manuscript. We also thank Fanny Abad and Camille Menard for their help in the coordination of the study and Matthieu Schoepfer for his comments on the manuscript.

Disclosures

None of the authors has any conflict of interest to disclose. 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.

References

1. Lin JJ, Mula M, Hermann BP. Uncovering the neurobehavioural comorbidities of epilepsy over the lifespan. *Lancet* 2012;380:1180–1192.
2. Hermann B, Jones J, Dabbs K, et al. The frequency, complications and aetiology of ADHD in new onset paediatric epilepsy. *Brain* 2007;130:3135–3148.
3. WHO. Epilepsy in the WHO European Region, 2010. Available at: http://www.ibe-epilepsy.org/downloads/EURO%20Report%20160510.pdf. Accessed February 15, 2016.
4. Sherman EM, Slick DJ, Connolly MB, et al. ADHD, neurological correlates and health-related quality of life in severe pediatric epilepsy. *Epilepsia* 2007;48:1083–1091.
5. Reilly C, Atkinson P, Das KB, et al. Neurobehavioral comorbidities in children with active epilepsy: a population-based study. *Pediatrics* 2014;133:e1586–e1593.
6. Torres AR, Whitney J, Gonzalez-Heydrich J. Attention-deficit/hyperactivity disorder in pediatric patients with epilepsy: review of pharmacological treatment. *Epilepsy Behav* 2008;12:217–233.
7. Fosi T, Lax-Pericall MT, Scott RC, et al. Methylphenidate treatment of attention deficit hyperactivity disorder in young people with learning disability and difficult-to-treat epilepsy: evidence of clinical benefit. *Epilepsia* 2013;54:2071–2081.
8. Gonzalez-Heydrich J, Whitney J, Waber D, et al. Adaptive phase I study of OROS methylphenidate treatment of attention deficit hyperactivity disorder with epilepsy. *Epilepsy Behav* 2010;18:229–237.
9. Gonzalez-Heydrich J, Hsin O, Gumlak S, et al. Comparing stimulant effects in youth with ADHD symptoms and epilepsy. *Epilepsy Behav* 2014;36:102–107.
10. Koneski JA, Casella EB, Agertt F, et al. Efficacy and safety of methylphenidate in treating ADHD symptoms in children and adolescents with uncontrolled seizures: a Brazilian sample study and literature review. *Epilepsy Behav* 2011;21:228–232.
11. Radziuk AL, Kieling RR, Santos K, et al. Methylphenidate improves the quality of life of children and adolescents with ADHD and difficult-to-treat epilepsies. *Epilepsy Behav* 2015;46:215–220.
12. Santos K, Palmini A, Radziuk AL, et al. The impact of methylphenidate on seizure frequency and severity in children with attention-deficit-hyperactivity disorder and difficult-to-treat epilepsies. *Dev Med Child Neurol* 2013;55:654–660.
13. Socanski D, Aurlien D, Herigstad A, et al. Attention deficit/hyperactivity disorder and interictal epileptiform discharges: it is safe to use methylphenidate? *Seizure* 2015;25:80–83.
14. ILAE. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* 1989;30:389–399.
15. American Psychiatric Association. *DSM-IV. Diagnostic and statistical manual of mental disorders, 4th ed . rev.: DSM-IV-R*. Washington, DC: American Psychiatric Association; 2000.
16. ANSM. Méthylphénidate: données d'utilisation et de sécurité d'emploi en France, 2013. Available at:http://ansm.sante.fr/var/ansm_site/storage/original/application/8dd1277a3867155547b4dce58fc0db00.pdf. Accessed February 12, 2016.
17. Faries D, Yalcin I, Harder D, et al. Validation of the ADHD rating scale as a clinician administrated and scored instrument. *J Atten Disord* 2001;5:107–115.
18. Zhang S, Faries DE, Vowles M, et al. ADHD Rating Scale IV: psychometric properties from a multinational study as a clinician-administered instrument. *Int J Methods Psychiatr Res* 2005;14:186–201.
19. EMA. Guideline on the clinical investigation of medicinal products for the treatment of attention deficit hyperactivity disorder (ADHD), 2008. European Medicine Agency. Available at:http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/08/WC500095686.pdf. Accessed February 15, 2016.
20. Johnson M, Ostlund S, Fransson G, et al. Omega-3/omega-6 fatty acids for attention deficit hyperactivity disorder: a randomized placebo-controlled trial in children and adolescents. *J Atten Disord* 2009;12:394–401.
21. Michelson D, Allen AJ, Busner J, et al. Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity

disorder: a randomized, placebo-controlled study. *Am J Psychiatry* 2002;159:1896–1901.
22. Michelson D, Faries D, Wernicke J, et al. Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, dose-response study. *Pediatrics* 2001;108:E83.
23. Michelson D, Buitelaar JK, Danckaerts M, et al. Relapse prevention in pediatric patients with ADHD treated with atomoxetine: a randomized, double-blind, placebo-controlled study. *J Am Acad Child Adolesc Psychiatry* 2004;43:896–904.
24. Madaan V, Daughton J, Lubberstedt B, et al. Assessing the efficacy of treatments for ADHD: overview of methodological issues. *CNS Drugs* 2008;22:275–290.
25. Mercier C, Roche S, Gaillard S, et al. Partial validation of a French version of the ADHD-rating scale IV on a French population of children with ADHD and epilepsy. Factorial structure, reliability, and responsiveness. *Epilepsy Behav* 2016;58:1–6.
26. Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. *N Engl J Med* 2010;362:790–799.
27. Hesdorffer DC, Ludvigsson P, Olafsson E, et al. ADHD as a risk factor for incident unprovoked seizures and epilepsy in children. *Arch Gen Psychiatry* 2004;61:731–736.
28. Chou IC, Chang YT, Chin ZN, et al. Correlation between epilepsy and attention deficit hyperactivity disorder: a population-based cohort study. *PLoS ONE* 2013;8:e57926.
29. Bechtel N, Kobel M, Penner IK, et al. Attention-deficit/hyperactivity disorder in childhood epilepsy: a neuropsychological and functional imaging study. *Epilepsia* 2012;53:325–333.
30. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. *Lancet* 2005;366:237–248.
31. Rappley MD. Clinical practice. Attention deficit-hyperactivity disorder. *N Engl J Med* 2005;352:165–173.
32. Storebo OJ, Krogh HB, Ramstad E, et al. Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials. *BMJ* 2015;351:h5203.
33. Gross-Tsur V, Manor O, van der Meere J, et al. Epilepsy and attention deficit hyperactivity disorder: is methylphenidate safe and effective? *J Pediatr* 1997;130:670–674.
34. Hemmer SA, Pasternak JF, Zecker SG, et al. Stimulant therapy and seizure risk in children with ADHD. *Pediatr Neurol* 2001;24:99–102.
35. Sanchez FernandezI, Loddenkemper T, Galanopoulou AS, et al. Should epileptiform discharges be treated? *Epilepsia* 2015;56:1492–1504.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Clinical determinants of severity of ADHD symptoms.

Table S2. ADHD Rating Scale-IV at baseline in patients receiving antiepileptic drug monotherapy.

Appendix S1. Investigators of the Paediatric Epilepsy REsearch NEtwork (PERENE).

Appendix S2. STROBE Statement—checklist of items that should be included in reports of observational studies.