Epilepsy & Behavior 101 (2019) 106543

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Attention-deficit hyperactivity disorder in adults with epilepsy☆

Nahid Ashjazadeh [a,b], Ali Sahraeian [c], Iman Sabzgolin [b,d], Ali A. Asadi-Pooya [a,e,*]

[a] Shiraz Neuroscience Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[b] Department of Neurology, Shiraz University of Medical Sciences, Shiraz, Iran
[c] Department of Psychiatry, Shiraz University of Medical Sciences, Shiraz, Iran
[d] Clinical Neurology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[e] Jefferson Comprehensive Epilepsy Center, Department of Neurology, Thomas Jefferson University, Philadelphia, PA, USA

ARTICLE INFO

Article history:
Received 10 June 2019
Revised 3 September 2019
Accepted 3 September 2019
Available online 4 November 2019

Keywords:
Adults
Attention-deficit hyperactivity disorder
Epilepsy
Seizure

ABSTRACT

Purpose: We investigated the prevalence of attention-deficit hyperactivity disorder (ADHD) in adult people with epilepsy (PWE). We hypothesized that ADHD is common among adult PWE and, some clinical factors may be associated with ADHD.

Methods: In this cross-sectional study, 200 adult PWE referred to our neurology clinic at Shiraz, Iran were recruited (consecutively sampled). Validated Persian versions of Adult ADHD Self-Report Scale (ASRS v1.1) and Addenbrooke's Cognitive Examination-Revised (ACE-R) tests were used. We performed univariate analyses and also a logistic regression analysis.

Results: Eighty-two patients (41%) were male, and 118 (59%) were female. Seventy patients (35%) had a positive screen for ADHD. There was a significant association between cognitive function and the prevalence of positive screening for ADHD in the whole group; 19 (18%) of the patients with a normal cognition, 23 (42%) of those with mild impairment, and 28 (70%) of those with severe cognitive impairment screened positive for ADHD ($p = 0.0001$). One hundred and five patients had normal cognition and were studied separately. Nineteen patients (18%) had screened positive for ADHD. Attention-deficit hyperactivity disorder was not associated with any of the tested variables in these patients.

Conclusion: About one-fifth of adults with epilepsy and normal cognitive function may have a positive screen for ADHD. Routine screening of all PWE for early detection and appropriate management of ADHD would be a reasonable approach.

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is described as a neurodevelopmental problem associated with inattention and/or hyperactivity and impulsivity [1]. This disorder mainly occurs in young ages, with a prevalence of 8–10% of children and adolescents [2]. Wrongfully, it is thought by many that most of young patients with ADHD recover during their adolescence; but there is now enough evidence that shows many of these patients continue to suffer from the disorder even during their adulthood. The prevalence of ADHD in adults is about 2–5% [3].

Epilepsy is a disorder of the brain. Most studies assessing the prevalence of ADHD in people with epilepsy (PWE) were performed in the pediatric populations, and they have found two to three times higher rates of ADHD in populations with epilepsy compared with that in controls [4–6]. In children with epilepsy, severity and frequency of seizures and an earlier age at the onset of seizures were common risk factors for suffering from ADHD [4–8]. However, studies on ADHD in adults with epilepsy are scarce. One study on adults with epilepsy found that ADHD symptoms occur in nearly one of five of these patients; ADHD was associated with increased psychosocial morbidity and lowered quality of life in PWE [9].

In this study, we aimed to investigate the prevalence of ADHD in adults with epilepsy. We also investigated potentially significant demographic and clinical factors that may be associated with ADHD in these patients. We hypothesized that ADHD is common among adult patients with epilepsy, and some clinical factors (*e.g.*, seizure frequency) may be associated with the presence of ADHD in adults with epilepsy. These data could add to our knowledge of comorbidities in PWE and may be important clinically and practically.

☆ The authors conducted the statistical analyses.

* Corresponding author at: Neuroscience Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.
E-mail addresses: sahraian@sums.ac.ir (A. Sahraeian), aliasadipooya@yahoo.com (A.A. Asadi-Pooya).

https://doi.org/10.1016/j.yebeh.2019.106543
1525-5050/

2. Materials and methods

In this cross-sectional study, 200 adult PWE referred to the Shiraz University of Medical Sciences neurology clinic or hospital were recruited (consecutively sampled). Inclusion criteria included the following: age >18 years; minimum level of literacy of 5 years; diagnosis of epilepsy by a board-certified neurologist based on the patients' clinical and electroencephalographic data. Exclusion criteria included the following: any known major psychiatric illnesses such as schizophrenia or severe mood disorders according to the patients' medical records and clinical judgment of the treating physician.

After obtaining a written informed consent from all the patients, their demographic and clinical data including sex, type of epilepsy [idiopathic (genetic) generalized epilepsy (*e.g.*, juvenile myoclonic epilepsy) *vs.* focal epilepsy syndrome (*e.g.*, temporal lobe epilepsy)], duration of epilepsy, antiepileptic drug (AED) therapy (polytherapy *vs.* monotherapy), and number of their seizures in the previous year (seizure-free *vs.* one or more seizures per months *vs.* less than one seizure per month) were collected. We used the validated Persian version of Adult ADHD Self-Report Scale (ASRS v1.1) questionnaire [10] to investigate and screen for ADHD in these patients. We also used the validated Persian version of Addenbrooke's Cognitive Examination-Revised (ACE-R) test [11] to assess their cognitive function; a cutoff point of 84 (a sensitivity of 93% and a specificity of 91%) was considered in discriminating mild cognitive impairment (MCI) from a healthy population, and a cutoff point of 78 (a sensitivity of 73% and a specificity of 93%) was used in differentiating MCI from severe cognitive impairment [11]. We compared PWE with a positive screening for ADHD with those who did not have a positive screening for ADHD according to their scores on the questionnaire. We arbitrarily categorized the patients according to their education [no college education (*i.e.*, 5–12 years of education) *vs.* college education (*i.e.*, >12 years of education)]. Initially, we performed univariate analyses using Pearson Chi-square. Variables that were significant ($p < 0.05$) in univariate analyses were assessed in a logistic regression. Odds ratio (OR) and 95% confidence interval (CI) were calculated. In a separate analysis, patients with cognitive decline were excluded. Pearson Chi-Square tests with Bonferroni correction were used for statistical analyses. A p-value less than 0.05 was considered as significant. This study was conducted with the approval by Shiraz University of Medical Sciences Review Board and Ethics Committee.

3. Results

Eighty-two patients (41%) were male, and 118 (59%) were female. Mean age (± standard deviation) of the patients was 31.5 (± 10.5) years (minimum 19 and maximum 67 years). Seventy patients (35%) had a positive screening test for ADHD and 130 patients (65%) did not. None of the patients had a previous diagnosis of ADHD, and none was taking any medication for ADHD. In terms of cognitive function as determined by the validated Persian version of ACE-R test, 105 patients (52.5%) had normal cognition, 55 people (27.5%) had MCI, and 40 (20%) had severe cognitive impairment. We examined the association between their cognitive function and the prevalence of positive screening for ADHD; 19 (18%) of the patients with a normal cognition, 23 (42%) of those with MCI, and 28 (70%) of the patients with severe cognitive impairment had positive screening for ADHD ($p = 0.0001$). In the whole cohort, a positive screen for ADHD was also associated with educational achievement (college education in 45% of those without ADHD and in 20% of those with ADHD; $p = 0.0001$) and AED regimen (polytherapy with AEDs in 39% of those without ADHD and in 57% of those with ADHD; $p = 0.01$) in univariate analyses. A positive screening for ADHD had no associations with sex, epilepsy duration, seizure control status, and epilepsy type ($p > 0.05$ for all comparisons). We then performed a logistic regression analysis, assessing the three significant variables. The model, which was generated by regression analysis, was significant ($p = 0.0001$) and could predict the possibility of a positive screening for ADHD in 71% of the patients. Within the model, educational achievement (negatively) (OR: 0.4; 95% CI: 0.21–0.95; $p = 0.03$) and cognitive function (MCI: OR: 2.6; 95% CI: 1.21–5.54; $p = 0.01$ and severe cognitive impairment: OR: 7.3; 95% CI: 3.01–17.70; $p = 0.0001$) retained their significance and showed association with a positive screen for ADHD.

One hundred and five patients had a normal cognition and were studied separately. Seventy patients (67%) were females, and 35 (33%) were males. Nineteen patients (18%) had a positive screen for ADHD. After Bonferroni correction for six tests, ADHD was not significantly associated with any of the tested variables (gender, educational achievement, epilepsy type, seizure control status, AED regimen, and duration of epilepsy) (Table 1).

4. Discussion

In this study, we observed that 18% of adults with epilepsy without cognitive impairment had a positive screen for ADHD; this is consistent with a previous study from the USA [9]; their rate was 18.4%. Studies on ADHD in adults with epilepsy are scarce; our study adds to the literature and highlights the significant possibility of ADHD comorbidity in adults with epilepsy. Replicating the findings from a Western study [9] in a Middle-Eastern study may suggest that the relationship between epilepsy and ADHD has neurobiological underpinnings. However, more information is needed before a conclusion regarding the cause of this association can be made. The prevalence of ADHD among PWE could vary across the world, and this should be investigated in well-designed future studies. The underlying brain disorder in PWE and also adverse effects of AEDs used by these patients are possible reasons for the high prevalence of ADHD in PWE. However, some studies have shown that interictal epileptiform activity in PWE may also affect cognitive performance. It seems that interictal spikes may directly disrupt the functional brain networks responsible for language, behavior, and cognition [12].

The apparent strong association of epilepsy with ADHD in the whole group may be artifactual, because of the difficulty in distinguishing ADHD from cognitive impairment (see below); however, an 18% rate of positive screening test for ADHD in patients with a normal cognitive function is significant. Considering the high prevalence of ADHD in PWE (in both adults and children), routine screening of all PWE for early detection and appropriate management of ADHD would be a reasonable

Table 1
Factors associated with a positive screen for ADHD in adults with epilepsy with normal cognition.

	Patients with ADHD (# 19)	Patients without ADHD (# 86)	p value*
Sex ratio (female:male)	15:4	55:31	0.2
College education	8 (42%)	45 (52%)	0.4
Seizure frequency (free *vs.* ≤1 per month *vs.* >1 per month)	6 (32%)/6 (32%)/7 (36%)	40 (47%)/22 (25%)/24 (28%)	0.4
Epilepsy duration (<1 year *vs.* 1–5 years *vs.* >5 years)	1 (5%)/7 (37%)/11 (58%)	3 (3%)/23 (27%)/60 (70%)	0.6
Epilepsy type (generalized *vs.* focal)	11 (58%)/8 (42%)	27 (31%)/59 (69%)	0.03
AED regimen (mono- *vs.* polytherapy)	9 (47%)/10 (53%)	60 (70%)/26 (30%)	0.1

Attention-deficit hyperactivity disorder: ADHD; antiepileptic drug: AED.
* Uncorrected p-value. After Bonferroni correction, the threshold for statistical significance is 0.008.

approach [13]. Attention-deficit hyperactivity disorder in adult PWE has been associated with increased psychosocial morbidity and lowered quality of life in a previous study [9], and its early detection and appropriate management may help improve the quality of life of the patients. Previous studies have also shown that adults with ADHD often have lower education and higher rates of unemployment than the general population [14,15]. We did not observe a significant association between ADHD and educational achievement in adults with epilepsy with normal cognitive function in our study. However, early detection and management of ADHD in PWE might help them achieve a better education. This should also be tested in future studies.

In designing any future studies on ADHD in patients with epilepsy, investigators should bear in mind that cognitive impairment and ADHD may have bidirectional relationships; while patients with cognitive impairment often also have attention impairment (attention is a component of cognition), ADHD can masquerade as cognitive impairment [16]. In this study, we observed that the frequency of a positive screen for ADHD increased with the degree of cognitive impairment significantly. However, identifying ADHD in the context of cognitive impairment or *vice versa* is difficult for the above reasons. Importantly, we were able to prove that our main hypothesis was correct, and ADHD is common among adult patients with epilepsy (by excluding patients with any cognitive impairment that might have cast a doubt on the findings if we had not done so).

This study has some limitations. For logistical reasons, we did not include a healthy control group. In addition, while we excluded patients with any known major psychiatric illnesses such as schizophrenia or mood disorders according to the patients' medical records and clinical judgment of the treating physician, we did not use psychological screening tests to investigate some important factors such as mild depression or anxiety, which may affect our results; there are many symptoms of ADHD that may fall under the diagnoses of mood and anxiety disorders. Similarly, data on AEDs have not been collected, and for this reason, it is not possible to clarify whether our findings are affected by side effects of medications.

In conclusion, about one-fifth of adults with epilepsy may have a positive screen for ADHD, and routine screening of all PWE for early detection and appropriate management of ADHD would be a reasonable approach.

Declaration of competing interest

Ali A. Asadi-Pooya, M.D.: Honoraria from Cobel Daruo, RaymandRad, and Sanofi; Royalty: Oxford University Press (Book publication). Others, M.D.: none.

Acknowledgments

We thank Shiraz University of Medical Sciences for supporting this study.

References

[1] American Psychiatric Association. DSM-5 Task Force. Diagnostic and statistical manual of mental disorders DSM-5. 5th ed.. Washington, DC: American Psychiatric Association; 2013.
[2] Williams AE, Giust JM, Kronenberger WG, Dunn DW. Epilepsy and attention-deficit hyperactivity disorder: links, risks, and challenges. Neuropsychiatr Dis Treat. 2016; 12:287–96.
[3] Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. I. Int J Epidemiol. 2014;43:434–42.
[4] Reilly C, Atkinson P, Das KB, Chin RF, Aylett SE, Burch V, et al. Neurobehavioral comorbidities in children with active epilepsy: a population-based study. Pediatrics. 2014;133:e1586–93.
[5] Cohen R, Senecky Y, Shuper A, Inbar D, Chodick G, Shalev V, et al. Prevalence of epilepsy and attention-deficit hyperactivity (ADHD) disorder: a population-based study. J Child Neurol. 2013;28(1):120–3.
[6] Choudhary A, Gulati S, Sagar R, Sankhyan N, Sripada K. Childhood epilepsy and ADHD comorbidity in an Indian tertiary medical center outpatient population. Sci Rep. 2018;8:2670.
[7] Sherman EM, Slick DJ, Connolly MB, Eyrl KL. ADHD, neurological correlates and health-related quality of life in severe pediatric epilepsy. Epilepsia. 2007;48: 1083–91.
[8] McCusker CG, Kennedy PJ, Anderson J, Hicks EM, Hanrahan D. Adjustment in children with intractable epilepsy: importance of seizure duration and family factors. Dev Med Child Neurol. 2002;44:681–7.
[9] Ettinger AB, Ottman R, Lipton RB, Cramer JA, Fanning KM, Reed ML. Attention-deficit/hyperactivity disorder symptoms in adults with self-reported epilepsy: results from a national epidemiologic survey of epilepsy. Epilepsia. 2015;56:218–24.
[10] Mokhtari H, Rabiei M, Salimi SH. Psychometric properties of the Persian version of Adult Attention-Deficit/Hyperactivity Disorder Self-Report Scale. Iran J Psychiatr Clin Psychol. 2015;21:244–53.
[11] Pouretemad HR, Khatibi A, Ganjavi A, Shams J, Zarei M. Validation of Addenbrooke's Cognitive Examination (ACE) in a Persian-speaking population. Dement Geriatr Cogn Disord. 2009;28:343–7.
[12] Asadi-Pooya AA, Forouzesh M, Eidi H, Mirzaghafour SE. Levetiracetam versus carbamazepine in treatment of rolandic epilepsy. Epilepsy Behav. 2019;94:1–8.
[13] Auvin S, Wirrell E, Donald KA, Berl M, Hartmann H, Valente KD, et al. Systematic review of the screening, diagnosis, and management of ADHD in children with epilepsy. Consensus paper of the Task Force on Comorbidities of the ILAE Pediatric Commission. Epilepsia. 2018;59:1867–80.
[14] Ebejer JL, Medland SE, van der Werf J, Gondro C, Henders AK, Lynskey M, et al. Attention deficit hyperactivity disorder in Australian adults: prevalence, persistence, conduct problems and disadvantage. PLoS One. 2012;7:e47404.
[15] Küpper T, Haavik J, Drexler H, Ramos-Quiroga JA, Wermelskirchen D, Prutz C, et al. The negative impact of attention-deficit/hyperactivity disorder on occupational health in adults and adolescents. Int Arch Occup Environ Health. 2012;85:837–47.
[16] Pierre M, Cogez J, Lebain P, Loisel N, Lalevée C, Bonnet AL, et al. Detection of adult attention deficit hyperactivity disorder with cognitive complaint: experience of a French memory center. Rev Neurol (Paris). 2019;175:358–66.