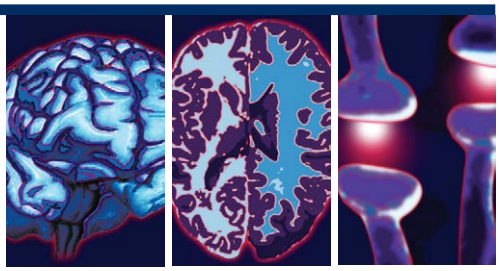

Electroencephalographic Abnormalities in Non-epileptic Children with Attention-Deficit /Hyperactivity Disorder

Yi-Wei Li[1], Hui-Ju Chen[2,†], Kun-Long Hung[1,3]

ABSTRACT

Objective: Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in childhood, however few studies have investigated epileptic seizures and electroencephalographic abnormalities in children with ADHD. The aim of this study was to explore the occurrence of epileptiform discharges in children with ADHD.

Method: We enrolled children with ADHD who visited the neurology clinic of our hospital between January 2014 and June 2016, all of whom met the DSM-V criteria and underwent awake and sleep electroencephalography examinations. We excluded those with histories of intellectual disabilities, epilepsy, congenital anomalies and substance abuse. None of the patients had a history of seizures before the examination.

Results: A total of 121 patients were included (93 males, 28 females, mean age 6.9±2.5 years), of whom 28 (23.1%) had electroencephalographic abnormalities, including three (10.7%) with generalized epileptiform discharges and 25 (89.3%) with focal epileptiform discharges. The focal epileptiform discharges were most prevalent from the rolandic area (15/25), followed by the parietal area (5/25), frontal area (4/25) and occipital area (1/25). Fourteen (50%) of the 28 patients had abnormal electroencephalographic findings only during sleep recordings.

Conclusions: Electroencephalographic focal abnormalities were found in 23.1% of our patients, of which 50% appeared only during sleep recordings. We suggest that sleep and awake electroencephalography recordings should be part of the routine assessment of children with ADHD regardless of whether or not they have overt seizures or other neurological conditions. In patients who do not respond well to traditional ADHD drugs, treatment for paroxysmal electroencephalographic abnormalities may be considered.

Keywords

Electroencephalography, Attention-deficit/hyperactivity disorder

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in childhood. It is characterized by symptoms of inattention, hyperactivity, and impulsivity, and occurs in 3-8% of school-aged children in the general population [1,2]. The reported prevalence of ADHD varies from 23% to 40% in children with epilepsy, compared to 3-6% of the general population [3,4]. A number of studies have reported a close association between ADHD and epilepsy [5-10]. Chou et al. [10] reported

[1]Department of Pediatrics, Cathay General Hospital, Taipei, Taiwan

[2]Department of Pediatric Neurology, MacKay Children's Hospital, Taipei, Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

[3]Department of Pediatrics, Fu Jen Catholic University Hospital, New Taipei, Taiwan

[†]Author for correspondence: Hui-Ju Chen, MD, Department of Pediatric Neurology, MacKay Children's Hospital, Taipei, Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, Tel: 886-2-25433535 ext. 3267; Fax: 886-2-25433642; email: hjuchen@ms65.hinet.net

that the hazard ratio of ADHD in children with epilepsy was 2.54 (95% confidence interval [CI], 2.02-3.18), while the hazard ratio of epilepsy in children with ADHD was 3.94 (95% CI, 2.58–6.03). The coexistence of ADHD and epilepsy suggests the possibility of overlapping neurodevelopmental pathways. Previous studies reported psychostimulants as the first-line treatment for ADHD children has risk of lowering seizure threshold in ADHD children with comorbid epilepsy. However, recent studies [11,12] have showed that psychostimulants are safe and effective in children with ADHD and concomitant active seizures or difficult-to treat epilepsies, but the choice of therapeutic strategies in this population was still controversial.

Electroencephalography (EEG) has been used to evaluate electrical activity in the brain for some time, and several studies have demonstrated a high incidence of epileptic seizures and EEG abnormalities in children with ADHD [13-17]. Hemmer et al. [13] reported the presence of epileptiform discharges in 36(15.4%) of 234 children with ADHD. Millichap et al. [16] examined 624 EEG records of children with ADHD and found abnormal discharges in 26.1%, and Lee et al. [17] reported epileptiform discharges in 29 (16.1%) of 180 patients with ADHD. Some researchers have investigated the localization of EEG abnormalities in children with ADHD. Hemmer et al. [13] reported rolandic spikes accounted for 40% of the abnormal EEGs in children with ADHD. Holtman et al. [18] reported a significantly higher frequency of rolandic spikes in children with ADHD compared to normal children. However, Zaimog˘lu et al. [19] reported that the occurrence of epileptiform abnormalities in patients with ADHD was higher in the frontal area (41.0%). Although several studies mentioned the relationship between ADHD, epilepsy and the EEG abnormalities, there is a lack of Asian studies on the role of the topic.

The aim of this study was to investigate the prevalence of electroencephalographic abnormalities in Asian children with ADHD and to analyze their EEG characteristics and localization.

Method

We conducted this retrospective study between January 2014 and June 2016 at our hospital in Taipei, Taiwan. We reviewed the medical records of patients aged from 3 to 18 years who were diagnosed with ADHD at our early intervention clinic or pediatric neurology clinic. Patients with any history of intellectual disabilities, epilepsy, seizures, substance abuse, congenital anomalies or other neurologic disorders were excluded. All of the patients met the ADHD criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. This study was approved by the Institutional Review Board of our hospital (IRB number: CGH-P105055).

Awake and sleep electroencephalographic examinations were performed in all of the enrolled children using 16 channel digital recording with an international 10-20 electrode system. Digital EEGs were recorded for at least 60 minutes during wakefulness and sleep. Hyperventilation and photic stimulation were included. All EEG recordings were interpreted by experienced pediatric neurologists and classified as being normal or abnormal. We defined EEG abnormalities as generalized epileptiform discharges and focal epileptiform discharges. Epileptiform discharges only occurring during sleep were also recorded. The origins of the focal epileptiform discharges were further divided into rolandic, parietal, frontal and occipital regions.

The chi-square test and independent t-test were used for comparison between the normal EEG group and the epileptiform group.

Results

One hundred and twenty-one patients diagnosed with ADHD were enrolled in this study, all of whom completed awake and sleep EEG examinations. Of the 121 patients, 93 (76.9%) were male and 28 (23.1%) were female, with ages ranging from 3 to 14 years (mean 6.9±2.5 years). None of them received any stimulant medication before. All patients were further divided into three ADHD subtypes: 29 (24%) were the primarily inattentive type, 3 (2.5%) were the primarily hyperactive/impulsive type, and 89 (73.5%) were the combined type of ADHD. Normal EEG recordings were found in 93 (76.9%) of the patients, and abnormal recordings in 28 (23.1%). Of the 28 patients with abnormal EEG recordings, 7 (25%) were the primarily inattentive type, 1 (3.6%) were the primarily hyperactive/impulsive type, and 20 (71.4%) were the combined type of ADHD. The proportion of girls in the epileptiform group was significantly higher than the normal EEG group (P=0.021). There were no significant differences in their mean age (P=0.559) and ADHD subtypes

(*P*=0.884) between the normal EEG and the epileptiform groups (**Table 1**). Among the group of abnormal EEG recordings, three (10.7%) had generalized epileptiform discharges and 25 (89.3%) had focal epileptiform discharges. The focal epileptiform discharges were most prevalent from the rolandic area (15/25), followed by the parietal area (5/25), frontal area (4/25) and occipital area (1/25). Among the 15 (12.4%) patients who had epileptiform discharges from the rolandic area, seven were from the right side, three from the left side, and five bilaterally. The characteristics of the awake and sleep EEG recordings are summarized in **Table 2**.

Half (14/28) of the abnormal EEG findings were found only during sleep recordings. Of these patients, 7 patients had abnormal sleep behaviors: 2 had sleep-disordered breathing, 3 had periodic limb movement disorder and 2 had night awakenings. The localizations of the these epileptiform discharges during sleep recordings included seven from the rolandic region, three from the parietal region, one from the frontal region, one from the occipital region, and two were generalized spikes. **Figures 1** and **2** present examples of the abnormal EEG findings.

Discussion

The prevalence of epileptiform discharges in patients with ADHD has been reported to range from 6.1% [15] to 53%, [20] which is much higher than that for healthy children (3.5%) [21]. The wide variation in the frequency of EEG abnormalities may be due to different research methods, duration of EEG, EEG activation, and the enrolled study subjects. In this retrospective study, the prevalence of EEG abnormalities among non-epileptic children with ADHD was 23.1%, which is similar to the average rate of eight studies (26.1%) summarized by Millichap et al. [16] Compared to studies with awake only [15] or a lack of EEG studies, [13] the prevalence of EEG abnormalities in the current study is higher. However, the prevalence of abnormal EEG recordings in the current study is lower than that in studies with prolonged sleep recordings [20] or sleep-deprived EEGs [14,16]. This suggests that the prevalence of epileptiform discharges may be positively correlated with the duration of sleep EEG. In addition, the high incidence of epileptiform discharges suggests that ADHD is a brain disorder arising from neurobiological abnormalities.

In the current study, 10.7% (3/28) of the EEG abnormalities were generalized and 89.3% (25/28) were focal discharges. The localization of these focal epileptiform discharges was most commonly from the rolandic area, followed by the parietal and frontal areas. Rolandic discharges were identified in 12.4% of our 121 patients with ADHD, which is higher than that reported

Table 1: The summary of normal EEG and epileptiform group in the children with ADHD

	Normal EEG group (n = 93)	Epileptiform group (n = 28)	*P* value
Age(years)	6.8±2.6	7.1±2.3	.559
Female(%)	17(18.3%)	11(39.3%)	.021
ADHD, inattentive type	22(23.7%)	7(25%)	.884

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; EEG, electroencephalography.

Table 2. The characteristics of awake and sleep EEG recordings in the children with ADHD.

EEG Findings	No. (n = 121)	%
Normal	93	76.9
Abnormal	28	23.1
Generalized epileptiform discharges	3	10.7
Focal epileptiform discharges	25	89.3
Rolandic region	15	60.0
Right	7	46.7
Left	3	20
Bilateral	5	33.3
Parietal region	5	20.0
Frontal region	4	16.0
Occipital region	1	4.0

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; EEG, electroencephalography.

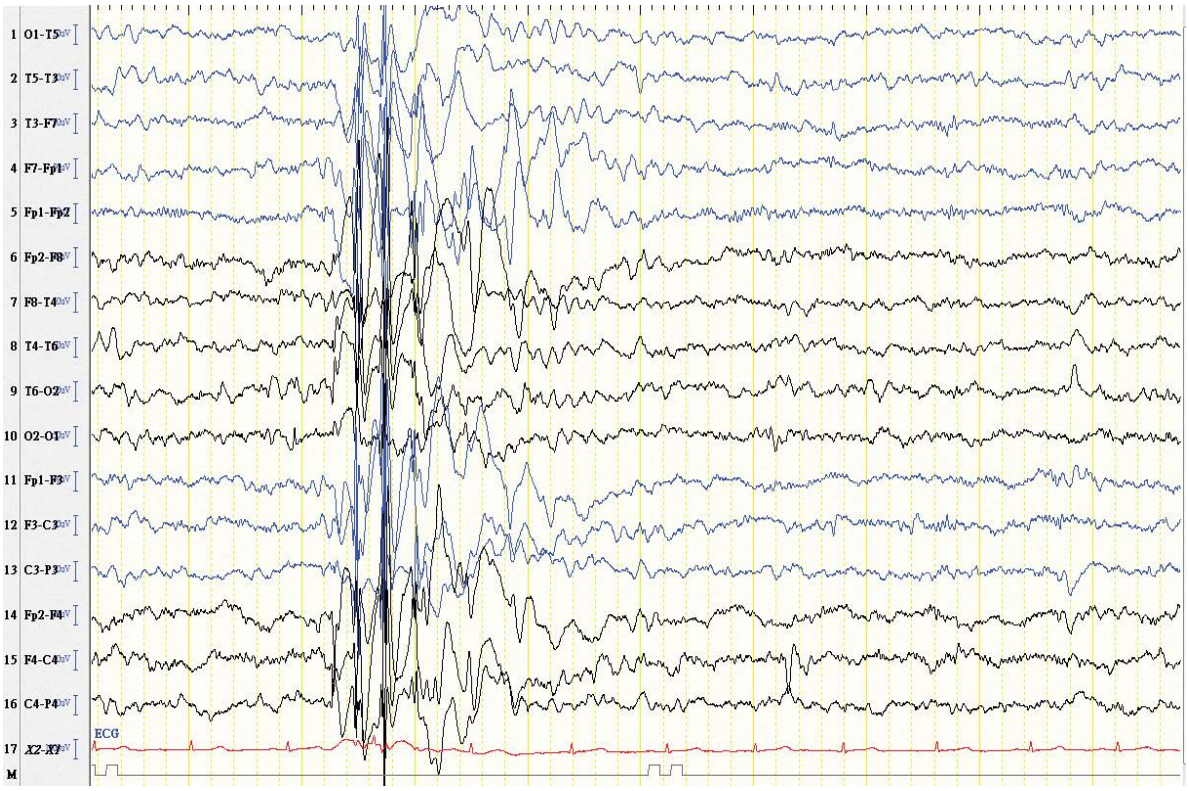

Figure 1: Paroxysmal bursts of high voltage spikes and spike-and-wave complexes over C4 with secondary generalization.

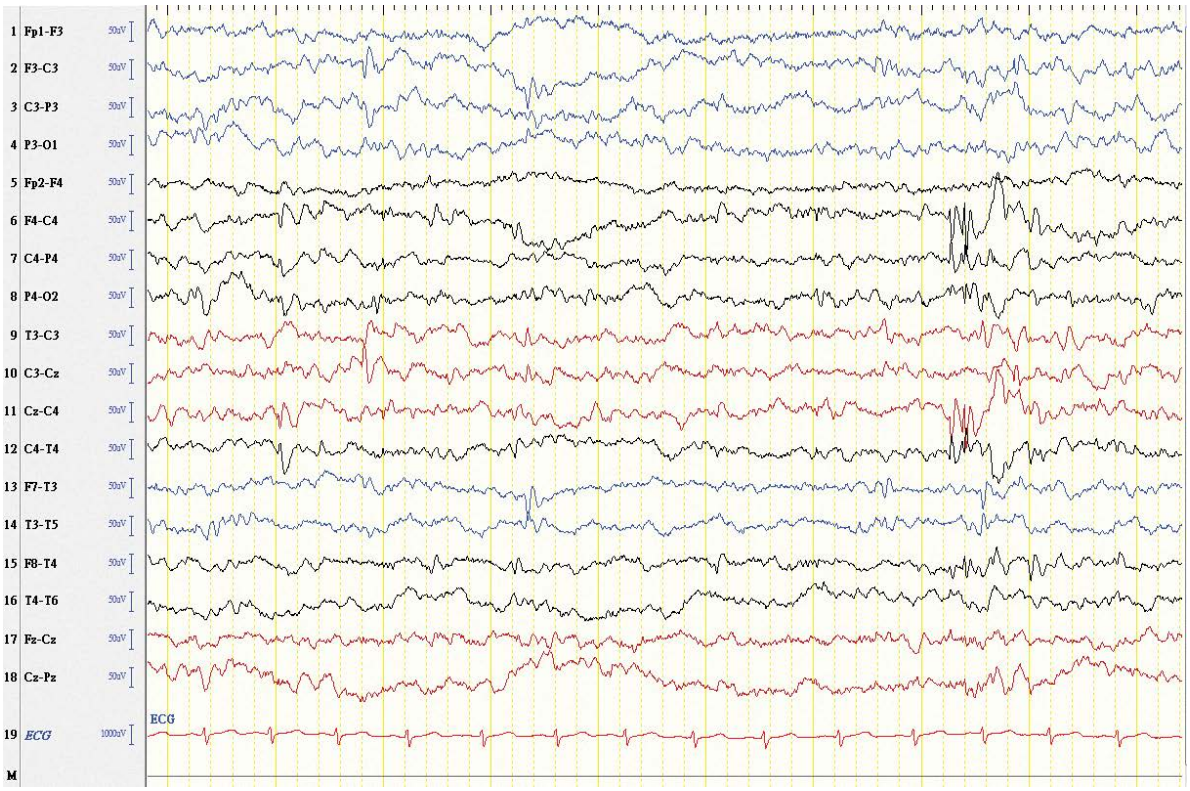

Figure 2: Paroxysmal spikes over bilateral centrotemporal regions alternatively during sleep recording.

by Holtmann et al. (5.6%) [18] and Zaimog˘lu et al. (7.4%) [19]. All of our subjects received awake and sleep EEG examinations, and this may explain the higher rate of rolandic spikes in our study. The role of rolandic spikes in patients with ADHD has been investigated by several authors. Some children with ADHD with rolandic spikes have been reported to demonstrate deficient inhibition of an ongoing response and decreased interference control causing increased impulsivity and deterioration in the course of ADHD [22]. Other studies have reported that children with rolandic spikes have difficulties in visual-spatial memory, phonologic awareness and delayed academic performance [23,24]. Although rolandic spikes have been reported to be one of the most common EEG abnormalities in children with ADHD and to be a cause of cognitive impairment, the mechanism between rolandic spikes and ADHD remains unclear.

Interestingly, 80% (12/15) of our children had rolandic discharges from the right side or bilaterally. This is similar to the report of Holtmann et al. [18] who found that right-sided or bilateral epileptiform discharges were most common in the children with ADHD with rolandic spikes. Several studies have reported that right hemispheric dysfunction is most likely to result in the symptoms of ADHD [25,26]. In addition, several structural [27,28] and functional [29,30] brain imaging studies have also demonstrated smaller and less activated anterior regions in the right hemisphere. Even though many studies support the hypothesis of right hemispheric involvement in ADHD, other studies have reported opposite results or different opinions. Therefore, further studies are needed in order to explore the association between brain networks and ADHD.

Of our patients, 50% (14/28) had epileptiform discharges only during sleep, and half of these patients had rolandic spikes. This is not surprising, since the amount of baseline brain rhythmicity differs considerably between sleep and wakefulness [31]. In a previous study, 24% of 176 children with ADHD showed focal paroxysmal abnormalities during sleep [14]. In addition, in the study by Silvestri et al. [20] 53.1% of the children with ADHD had epileptiform discharges, mostly in the centrotemporal region, during polysomnography, compared with only 18.7% of children with ADHD with standard abnormal EEG recordings. A review of eight published reports also showed a significantly higher prevalence of epileptiform abnormalities in non-epileptic children with ADHD in sleep EEG recordings compared to wake-only recordings [16,32]. It is reasonable that the frequency of EEG abnormalities is not proportional to clinical seizures. Epileptiform discharges during awake and sleep recordings in children with ADHD may suggest subclinical seizures or subsequent seizures. Hemmer et al. [13] reported seizures in three of 30 children with ADHD with epileptiform discharges compared to one of 175 children without epileptiform discharges. Another study reported a predictive value of epileptiform abnormalities for the subsequent development of seizures in children with ADHD of 14% [15]. In a recent study, four of 29 patients with ADHD with epileptiform discharges developed new-onset epilepsy at an interval from 3 to 61 months [17]. Therefore, children with ADHD with abnormal EEG recordings should receive long-term clinical follow-up and be carefully evaluated for subclinical seizures or the new onset of seizures.

A few studies have reported that patients with ADHD with subclinical epileptiform discharges experience improvements in cognitive function and ADHD behavior after taking antiepileptic drugs. In two observational studies [33,34] valproate sodium therapy remarkably decreased the clinical symptoms of ADHD, and in a retrospective study by Bakke et al. [35] 22 of 35 patients with ADHD showed a more than 50% reduction in spike index after levetiracetam treatment, including 59% with improvements in behavior. However, the use of antiepileptic drugs in children with ADHD is controversial, and further prospective studies are necessary to clarify this issue.

There are several limitations to this study. First, the small sample size from a single hospital. Second, we did not perform stratified analysis between the subtypes and severity of ADHD and the epileptiform discharges of various brain origin due to the limited sample size. Third, our study subjects were predominately male and of the mixed presentation. It is still a matter of debate whether the ADHD subtypes defined in DSM-IV are in fact facets of the same condition, especially since the initial subtype differences in inattention symptoms often diminish as children progress from preschool to elementary years [36]. Furthermore, there are important differences in symptomatology between boys and girls with ADHD [37]. Further studies are warranted to explore the relationship between EEG characteristics and ADHD subtypes.

In conclusion, the children with ADHD in this study had a significantly higher prevalence of epileptiform abnormalities than healthy children. Focal epileptiform discharges, mainly from the rolandic area, were the most common EEG abnormality, and half of the EEG abnormalities occurred only in sleep EEG recordings. We suggest that awake and sleep EEG examinations may provide a greater detection rate of epileptiform discharges in patients with ADHD than awake EEG only. When psychostimulants and non-stimulants [38] are not effective in patients with ADHD, awake and sleep EEG examinations or treatment for subclinical epileptiform discharges should be considered. For children with ADHD with EEG abnormalities, the subsequent onset of seizures in later life should be closely monitored. Children with ADHD with abnormal EEG recordings could be a risk factor for developing epilepsy in the future.

References

1. Trull TJ, Verges A, Wood PK, *et al.* The structure of Diagnostic and Statistical Manual of Mental Disorders (4th edition, text revision) personality disorder symptoms in a large national sample. *Personal. Disord* 3(4), 355-369 (2012).
2. Steinhausen HC. The heterogeneity of causes and courses of attention-deficit/hyperactivity disorder. *Acta. Psychiatr. Scand* 120(5), 392-399 (2009).
3. Cohen R, Senecky Y, Shuper A, *et al.* Prevalence of epilepsy and attention-deficit hyperactivity (ADHD) disorder: a population-based study. *J. Child. Neurol* 28(1), 120-123 (2013).
4. Dunn DW, Austin JK, Harezlak J, *et al.* ADHD and epilepsy in childhood. *Dev. Med. Child. Neurol* 45(1), 50-54 (2003).
5. Dunn DW, Austin JK, and Huster GA. Behaviour problems in children with new-onset epilepsy. *Seizure* 6(4), 283-287 (1997).
6. Kanner AM. The use of psychotropic drugs in epilepsy: what every neurologist should know. *Semin. Neurol* 28(3), 379-388 (2008).
7. Kirov R, Kinkelbur J, Banaschewski T, *et al.* Sleep patterns in children with attention-deficit/hyperactivity disorder, tic disorder, and comorbidity. *J. Child. Psychol. Psychiatry* 48(6), 561-570 (2007).
8. Malow BA. The interaction between sleep and epilepsy. *Epilepsia* 48 Suppl 9, 36-38 (2007).
9. Parisi P, Moavero R, Verrotti A, *et al.*, Attention deficit hyperactivity disorder in children with epilepsy. *Brain Dev* 32(1), 10-16 (2010).
10. Chou IC, Chang YT, Chin ZN, *et al.* Correlation between epilepsy and attention deficit hyperactivity disorder: a population-based cohort study. *PLoS. One* 8(3), e57926 (2013).
11. Gucuyener K, Erdemoglu AK, Senol S, *et al.* Use of methylphenidate for attention-deficit hyperactivity disorder in patients with epilepsy or electroencephalographic abnormalities. *J. Child. Neurol* 18(2), 109-112 (2003).
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* 55(7), 654-660 (2013).
13. Hemmer SA, Pasternak JF, Zecker SG, *et al.* Stimulant therapy and seizure risk in children with ADHD. *Pediatr. Neurol* 24(2), 99-102 (2001).
14. Hughes JR, DeLeo AJ, and Melyn MA. The Electroencephalogram in Attention Deficit-Hyperactivity Disorder: Emphasis on Epileptiform Discharges. *Epilepsy. Behav* 1(4), 271-277 (2000).
15. Richer LP, Shevell MI, and Rosenblatt BR. Epileptiform abnormalities in children with attention-deficit-hyperactivity disorder. *Pediatr. Neurol* 26(2), 125-129 (2002).
16. Millichap JJ, Stack CV, and Millichap JG. Frequency of epileptiform discharges in the sleep-deprived electroencephalogram in children evaluated for attention-deficit disorders. *J. Child. Neurol* 26(1), 6-11 (2011).
17. Lee EH, Choi YS, Yoon HS, *et al.* Clinical Impact of Epileptiform Discharge in Children With Attention-Deficit/Hyperactivity Disorder (ADHD). *J. Child. Neurol* 31(5), 584-588 (2016).
18. Holtmann M, Becker K, Kentner-Figura B, *et al.* Increased frequency of rolandic spikes in ADHD children. *Epilepsia* 44(9), 1241-1244 (2003).
19. Zaimoglu S, Turkdogan D, Mazlum B, *et al.* When Is EEG Indicated in Attention-Deficit/Hyperactivity Disorder? *J. Child. Neurol* 30(13), 1785-1793 (2015).
20. Silvestri R, Gagliano A, Calarese T, *et al.* Ictal and interictal EEG abnormalities in ADHD children recorded over night by video-polysomnography. *Epilepsy. Res* 75(2-3), 130-137 (2007).
21. Kaufmann R, Goldberg-Stern H, and Shuper A, Attention-deficit disorders and epilepsy in childhood: incidence, causative relations and treatment possibilities. *J. Child. Neurol* 24(6), 727-733 (2009).
22. Holtmann M, Matei A, Hellmann U, *et al.* Rolandic spikes increase impulsivity in ADHD - a neuropsychological pilot study. *Brain. Dev* 28(10), 633-640 (2006).
23. Northcott E, Connolly AM, McIntyre J, *et al.* Longitudinal assessment of neuropsychologic and language function in children with benign rolandic epilepsy. *J. Child. Neurol* 21(6), 518-522 (2006).
24. Pinton F, Ducot B, Motte J, *et al.* Cognitive functions in children with benign childhood epilepsy with centrotemporal spikes (BECTS). *Epileptic. Disord* 8(1), 11-23 (2006).
25. Stefanatos GA and Wasserstein J. Attention deficit/hyperactivity disorder as a right hemisphere syndrome. Selective literature review and detailed neuropsychological case studies. *Ann. N Y. Acad. Sci* 931, 172-195 (2001).
26. Song Y and Hakoda Y. The interference of local over global information processing in children with attention deficit hyperactivity disorder of the inattentive type. *Brain. Dev* 34(4), 308-317 (2012).
27. Almeida LG, Ricardo-Garcell J, Prado H, *et al.* Reduced right frontal cortical thickness in children, adolescents and adults with ADHD and its correlation to clinical variables: a cross-sectional study. *J. Psychiatr. Res* 44(16), 1214-1223 (2010).
28. Frodl T and Skokauskas N. Meta-analysis of structural MRI studies in children and adults with attention deficit hyperactivity disorder indicates treatment effects. *Acta. Psychiatr. Scand* 125(2), 114-126 (2012).
29. Hart H, Radua J, Nakao T, *et al.* Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. *JAMA. Psychiatry* 70(2), 185-198 (2013).
30. McCarthy H, Skokauskas N, Frodl T. Identifying a consistent pattern of neural function in attention deficit hyperactivity disorder: a meta-analysis. *Psychol. Med* 44(4), 869-880 (2014).
31. Bazil CW. Epilepsy and sleep disturbance. *Epilepsy. Behav.* 4 Suppl 2, S39-45 (2003).

32. Millichap JG, Millichap JJ, Stack CV. Utility of the electroencephalogram in attention deficit hyperactivity disorder. *Clin. EEG. Neurosci* 42(3), 180-184 (2011).

33. Gordon K, Bawden H, Camfield P, *et al.* Valproic acid treatment of learning disorder and severely epileptiform EEG without clinical seizures. *J. Child. Neurol* 11(1), 41-43 (1996).

34. Miyazaki M, Ito H, Saijo T, *et al.* Favorable response of ADHD with giant SEP to extended-release valproate. *Brain. Dev* 28(7), 470-472 (2006).

35. Bakke KA, Larsson PG, Eriksson AS, *et al.* Levetiracetam reduces the frequency of interictal epileptiform discharges during NREM sleep in children with ADHD. *Eur. J. Paediatr. Neurol* 15(6), 532-538 (2011).

36. Lahey BB, Pelham WE, Loney J, *et al.* Instability of the DSM-IV Subtypes of ADHD from preschool through elementary school. *Arch. Gen. Psychiatry* 62(8), 896-902 (2005).

37. Ng QX, Ho CYX, Chan HW, *et al.* Managing childhood and adolescent attention-deficit/hyperactivity disorder (ADHD) with exercise: A systematic review. *Complement. Ther. Med* 34, 123-128 (2017).

38. Ng QX. A Systematic Review of the Use of Bupropion for Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. *J. Child. Adolesc. Psychopharmacol* 27(2), 112-116 (2017).