



Autism spectrum disorder and attention-deficit/hyperactivity disorder-related symptoms in benign childhood epilepsy with centrotemporal spikes: A prospective case–control study

Gonca Bektaş^{a,*}, Uğur Tekin^b, Edibe Pembegül Yıldız^c, Nur Aydınlı^d, Mine Çalışkan^d, Meral Özmen^d

^a Division of Pediatric Neurology, Department of Pediatrics, Bakırköy Dr. Sadi Konuk Research and Training Hospital, Istanbul, Turkey

^b Department of Child and Adolescent Psychiatry, Bakırköy Dr. Sadi Konuk Research and Training Hospital, Istanbul, Turkey

^c Division of Pediatric Neurology, Department of Pediatrics, Kanuni Sultan Süleyman Training and Research Hospital, Istanbul, Turkey

^d Department of Pediatric Neurology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

ARTICLE INFO

Article history:

Received 7 February 2019

Revised 24 March 2019

Accepted 27 March 2019

Available online 23 April 2019

Keywords:

Behavior

Child

Rolandic

Seizure

ABSTRACT

Background: Benign childhood epilepsy with centrotemporal spikes (BECTS), one of the most common idiopathic epilepsy syndromes in children, has been associated with neuropsychological problems.

Purpose: The objective of this study was to investigate the frequency of symptoms related to comorbid neurodevelopmental disorders, the autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) in children with typical BECTS, and to identify corresponding risk factors.

Methods: Children and adolescents with typical BECTS aged 6–16 years were included in the study period from January 1, 2017, to December 31, 2017. Children with atypical presentations of BECTS, other neurological disorders, and preexisting neuropsychiatric disorders were excluded. The ASD and ADHD were assessed by the Social Communication Questionnaire (SCQ) and the Turgay Diagnostic and Statistical Manual of Mental Disorders – 4th Edition – Disruptive Behavior Disorders Rating Scale (T-DSM-IV-S), respectively. Patients' scores were compared with those of healthy subjects. Correlation analyses were performed to evaluate the association between the age at seizure onset, the total number of seizures and the SCQ and T-DSM-IV-S scores.

Results: Fifty-eight children with BECTS and 60 healthy children participated in the study. The total SCQ score, the SCQ reciprocal social interaction score, and the SCQ communication score significantly differed between children with BECTS and the control group ($p = 0.001$, $p < 0.001$, $p = 0.001$, respectively). The total ADHD score was significantly different between patients and controls ($p < 0.001$). A significant difference was observed between patients and controls in terms of the T-DSM-IV-S hyperactivity–impulsivity score and the T-DSM-IV-S inattention score ($p = 0.012$, $p < 0.001$, respectively). The age at seizure onset was significantly correlated with the total SCQ score ($p = 0.03$). The Spearman's correlation coefficient was 0.352 for the total SCQ score, indicating a positive association between the age at seizure onset and the total SCQ score.

Conclusion: Children with typical BECTS may have an increased risk of suffering from symptoms of ASD and ADHD. Children with late onset of seizures may be more likely to develop neuropsychological disturbances regarding ASD and ADHD.

© 2019 Elsevier Inc. All rights reserved.

1. Introduction

Benign childhood epilepsy with centrotemporal spikes (BECTS), one of the most common idiopathic epilepsy syndromes in children, is characterized by a benign course in terms of seizure control [1]. However, it was proposed that children with BECTS may develop neuropsychological problems [2].

Benign childhood epilepsy with centrotemporal spikes is considered as a neurodevelopmental disorder [3]. Both autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are highly comorbid neurodevelopmental disorders, with some shared phenotypic features [4]. It has been suggested that neurodevelopmental disorders, epilepsy, ASD, and ADHD share pathogenic mechanisms [5].

The studies evaluating neuropsychological outcomes in children with BECTS were focused on either ASD or ADHD only. Additionally, most of these studies were comprised of children with atypical BECTS, characterized by poor neuropsychological outcomes. Atypical BECTS is characterized by atypical forms of seizures, such as earlier age of onset

* Corresponding author at: Division of Pediatric Neurology, Department of Pediatrics, Bakırköy Dr. Sadi Konuk Research and Training Hospital, Istanbul 34147, Turkey.
E-mail address: gonca.bektas@istanbul.edu.tr (G. Bektaş).

or prolonged seizures, and atypical electroencephalography (EEG) findings [6–12].

This study aimed at identifying the frequency of symptoms regarding comorbid neurodevelopmental disorders, ASD and ADHD, in children with typical BECTS, and whether there is a relationship between symptoms of ASD and ADHD and clinical features of BECTS. We hypothesized that some of the features of ASD and ADHD may cooccur with typical BECTS, based on the shared pathogenic mechanisms.

2. Methods

This was a single-center prospective case–control study consisting of patients with BECTS followed up by the pediatric neurology outpatient clinic at the Istanbul Faculty of Medicine, Department of Pediatric Neurology from January 1, 2017, to December 31, 2017.

2.1. Participants

Children and adolescents with BECTS aged 6–16 years were included in the study if they had a typical seizure semiology, benign epileptic discharges as defined by the International League Against Epilepsy, unremarkable brain magnetic resonance imaging findings, and normal neurological examinations [13]. The exclusion criteria were as follows: (1) children with atypical presentations of BECTS as defined by Parisi and colleagues, (2) the presence of other neurological disorders, and (3) preexisting neuropsychiatric disorders [6]. Healthy subjects matched by age, sex, and socioeconomic status constituted the control group.

The study was reviewed and approved by the Institutional Ethics Committee at the Istanbul Faculty of Medicine. All participants and their legal representatives provided written informed consent and assent.

2.2. Clinical data

Demographic features, the age at seizure onset, the total number of seizures, the used antiepileptic drugs, and EEG findings were abstracted from individual and caregivers' interviews and medical records. The EEG recordings during sleep and awake were obtained according to the 10–20 international system of electrode placement.

2.3. Neuropsychological evaluation

All participants underwent an evaluation of neuropsychological functioning by utilizing standardized assessment batteries. Autism spectrum disorder and ADHD were assessed by the Social Communication Questionnaire (SCQ) and the Turgay Diagnostic and Statistical Manual of Mental Disorders – 4th Edition – Disruptive Behavior Disorders Rating Scale (T-DSM-IV-S), respectively. Both of them were completed by parents.

The SCQ is a 40-item questionnaire evaluating symptomatology associated with ASD. It was found to be a reliable and valid tool for evaluating the symptoms of ASD in children and adolescents aged 4–18 years [14–16]. We used the SCQ Lifetime Form that also assesses behaviors between 4 and 5 year olds. There are 3 subscales: (1) reciprocal social interaction, (2) communication, and (3) restricted, repetitive, stereotyped patterns of behavior. Each item scores like 0 or 1 point based on the absence or presence of abnormal behaviors. Total scores range from 0 to 39; anything above the threshold of 15 indicates an increased likelihood of ASD.

The T-DSM-IV-S is a questionnaire assessing hyperactivity/impulsivity, inattention, opposition–defiance, and conduct disorder symptoms. It has been shown to be reliable and valid for evaluating ADHD [17, 18]. Hyperactivity–impulsivity (9 items), inattention (9 items), and total ADHD (18 items) scores from the T-DSM-IV-S were utilized. Each question was scored based on the severity of symptom from 0 to 3 points, in which higher scores indicate greater psychopathology. On the other hand, each item was qualified as negative (0 and 1 point) or positive (2 and 3 points) to classify ADHD subtypes. When more than

5 out of 9 items were positive for one of the subscales, ADHD was classified as predominantly hyperactivity/impulsivity or predominantly inattentiveness. If the total number of positive items was 12 and above, then the ADHD was classified as combined type.

2.4. Data analysis

All statistical analyses were applied using SPSS Statistics for Windows version 16.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to determine whether variables were normally distributed. Demographic and clinical features were assessed using independent samples *t*-tests in case of normality and homogeneity of variances, or Mann–Whitney *U* tests otherwise. The Spearman's correlation coefficient analyses were performed to evaluate the association between the age at seizure onset, the total number of seizures, and the scores of SCQ and T-DSM-IV-S. The value of $p < 0.05$ was accepted as statistically significant.

3. Results

3.1. Participants' descriptive characteristics

A total of 118 participants, 58 children with BECTS and 60 healthy children, were analyzed. The mean age of the patients was 11.4 years (standard deviation [SD] 2.5; range 7–16 years), and the mean age of the controls 11.3 years (SD 3; range 6–17 years). There was no difference in the ages of patients and controls ($p = 0.9$). There was no gender predominance among patients (29 females to 29 males) and controls (30 females to 30 males). The mean age at seizure onset was 8.5 years (SD 2.5; range 4–13 years), and the mean duration of epilepsy was 2.9 years (SD 2.3; range 0.5–9 years).

Currently prescribed antiepileptic medications were levetiracetam in 20 (34%), valproic acid in 17 (29%), oxcarbazepine in 12 (21%), and carbamazepine in 3 (5%). Six out of 58 patients were receiving no medication. None of them were treated with more than one antiepileptic drug. The demographic and clinical characteristics of patients with BECTS are provided in Table 1.

3.2. Neuropsychological evaluation

The mean total SCQ score was 8.5 (SD 4.6; range 0–19) and 5.1 (SD 4.4; range 0–17) in the patient and control group, respectively. The total SCQ score, the SCQ reciprocal social interaction score, and the SCQ communication score significantly differed between children with BECTS and the control group ($p = 0.001$, $p < 0.001$, $p = 0.001$, respectively). The SCQ restricted interest score was not significantly different between the patients and the control group ($p = 0.46$). The total SCQ score was above the cutoff value in 6 out of 58 patients (10%), and in 1 out of 55 healthy children (2%).

Table 1
Demographic and clinical characteristics of patients with BECTS.

	Children with BECTS <i>n</i> = 58
The mean age, years (SD) range	11.4 (2.5) 7–16
Sex, <i>n</i> (%)	29 F (58)
The mean age at seizure onset, years (SD) range	8.5 (2.5) 4–13
The mean duration of epilepsy, years (SD) range	2.9 (2.3) 0.5–9
Current antiepileptic drugs, <i>n</i> (%)	
Levetiracetam	20 (34)
Valproic acid	17 (29)
Oxcarbazepine	12 (21)
Carbamazepine	3 (5)
No medication	6 (10)

Abbreviations: BECTS = benign childhood epilepsy with centrotemporal spikes; SD = standard deviation.

Table 2

The SCQ and ADHD scores of children with BECTS and healthy controls.

		Children with BECTS	Healthy controls	<i>p</i>
Total SCQ score	Mean (SD) Range	8.5 (4.6) 0–19	5.1 (4.3) 0–17	0.001
Reciprocal interaction score		2.7 (2.2) 0–9	1.3 (2) 0–9	0.000
Communication score		3.9 (2.3) 0–9	2.2 (1.9) 0–7	0.000
Restricted interests score		1.7 (1.7) 0–7	1.5 (1.8) 0–6	0.46
Total ADHD score		13.1 (9.7) 0–39	5.5 (4.3) 0–13	0.000
Hyperactivity–impulsivity score		6.7 (5.6) 0–18	2.7 (2.4) 0–8	0.012
Inattention score		6.6 (6.1) 0–26	2.9 (2.6) 0–10	0.000

Abbreviations: ADHD = attention-deficit and hyperactivity disorder; BECTS = benign childhood epilepsy with centrotemporal spikes; SCQ = Social Communication Questionnaire; SD = standard deviation.

The total ADHD score was significantly different between the patients and the control group ($p < 0.001$). A significant difference was observed between the patients and the control group in terms of the T-DSM-IV-S hyperactivity–impulsivity score and the T-DSM-IV-S inattention score ($p = 0.012$, $p < 0.001$, respectively). Eleven out of 58 (19%) children with BECTS were found to be at risk of having ADHD; 5 of them had predominantly hyperactivity/impulsivity; 5 of them had predominantly inattentiveness, and one had a combined-type ADHD (Table 2).

Bivariate relationships between the age at seizure onset, the total number of seizures, and the scores of the SCQ and T-DSM-IV-S were assessed. The age at seizure onset was significantly correlated with the total SCQ score ($p = 0.009$). The Spearman's correlation coefficient was 0.352 for the total SCQ score, indicating a positive association between the age at seizure onset and the total SCQ score (Fig. 1). There was no correlation between the total number of seizures and the scores of the SCQ and T-DSM-IV-S ($p > 0.05$).

4. Discussion

In this study, it was found that the symptoms of ASD and ADHD are more common in children with BECTS compared to healthy controls. The total SCQ scores and subscores for reciprocal social interaction and communication were higher in children with BECTS. The higher

percentages of children with BECTS had total SCQ scores above the cut-off value, which indicates a higher risk of having ASD. Also, children with BECTS had higher total ADHD scores with subscores of hyperactivity–impulsivity and inattention. Regarding the clinical features of BECTS, the older age at seizure onset was found to have an association with more frequent neurodevelopmental psychiatric symptoms in children with BECTS.

It is considered that ASD and epilepsy shared the molecular pathophysiology that leads to an imbalance between excitation and inhibition mechanisms [5]. Increased excitation of local neural circuits, responsible for seizures, has suggested that result in excessive perception, attention, and memory are the core symptoms of ASD [19]. The common coexistence of ASD and epilepsy in children favor the hypothesis of shared pathophysiology [20].

Among children with epilepsy, the prevalence of ASD was reported as 15–32% regardless of the epilepsy syndrome. Most of the studies evaluating the prevalence of ASD in children with epilepsy, comprised of a heterogeneous patient population with underlying diseases other than epilepsy that were shown to be closely related with ASD [7,8,20]. The results of these studies made interpretation difficult in terms of a direct relationship between a certain epilepsy syndrome and ASD.

Benign childhood epilepsy with centrotemporal spikes was suggested to lie on a phenotypic spectrum, begun to identify genetic basis, from typical BECTS to atypical BECTS, continuous spike and

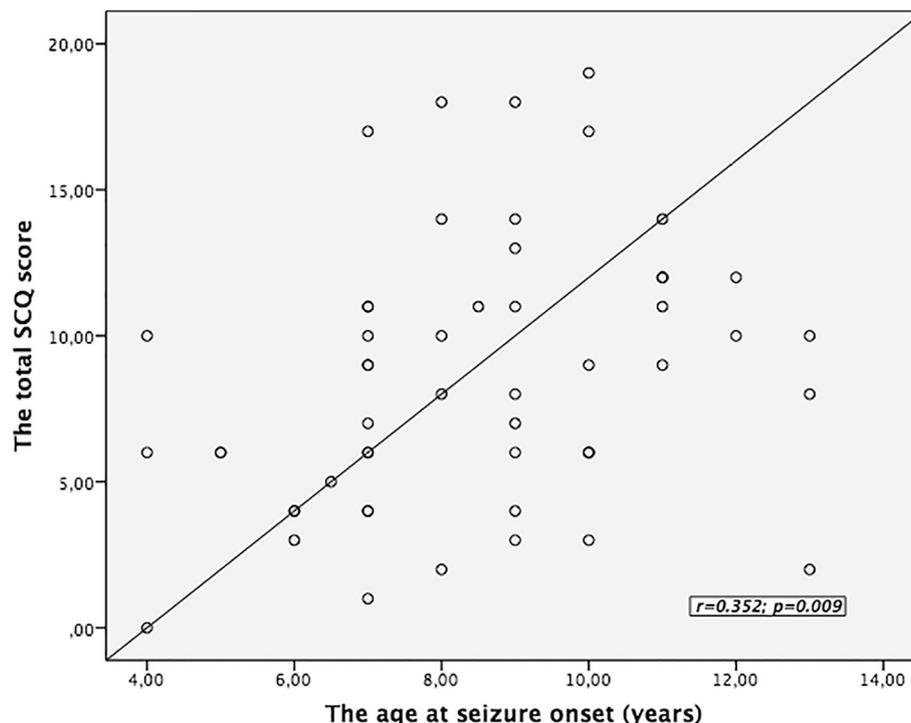


Fig. 1. Scatter plot showing the relationship between the age at seizure onset and the total SCQ score.

wave during slow-wave sleep, and the Landau–Kleffner syndrome. Features of autism were well-defined in this spectrum, except in children with typical BECTS [1,6,21,22]. However, we found that 10% of children with typical BECTS suffered from symptoms of autism, which was significantly higher than that with the enrolled healthy controls and also with the worldwide prevalence of ASD (1–2%) [23–26]. Children with BECTS exhibited impairment in reciprocal social interaction and communication rather than restricted interests.

Several authors have suggested that symptoms of ADHD may develop in children with BECTS [1,10–12,27]. We found that 19% of the children with typical BECTS had a high risk of having ADHD. This was much higher than the general prevalence of ADHD (3–7%) [28]. The reported prevalence of ADHD was so high as 65.6% in children with BECTS. It was suggested that the selection bias and the lack of structured interview or scales may have influenced the reported prevalence of ADHD [11,12]. Additionally, unlike the previous studies, the patient population in this study consisted of patients with typical BECTS who were less likely to have a worse neurophysiological outcome. This could elucidate the reason of low prevalence in this study compared with that of previous studies. It is noteworthy to state that children with typical BECTS have also a higher risk of having ADHD.

Our results show that children with BECTS suffering from the late onset of seizures were found to be more likely to have a higher risk of neurodevelopmental disturbances, consistent with previous reports [9, 29]. In the point of view of developmental neuropsychiatric pathophysiology, the emergence of epileptic activity in a time frame expected to the development of specific networks may lead to atypical neural connectivity that has been suggested as the underlying pathogenesis of ASD and ADHD [4,29]. This hypothesis could explain the influence of age at seizure onset on neuropsychological disturbances in children with BECTS.

This study has certain limitations. The first one is the small sample size. The second limitation is the lack of confirmatory diagnostic evaluations to make an accurate diagnosis of ADHD and ASD besides screening tools. Thirdly, we did not check sleep disruption, which may be associated with behavioral impairment in children with epilepsy [30–32]. Studies that are utilized polysomnographic evaluation can be helpful for investigating the effects of the possible sleep alterations. Finally, a long-term follow-up is needed to identify whether neuropsychological problems persist during adulthood.

5. Conclusion

Children with typical BECTS may have an increased risk of suffering from symptoms of ASD and ADHD. Children with late onset of seizures may be more likely to develop neuropsychological disturbances regarding ASD and ADHD. All children with BECTS should be screened for accompanying neurodevelopmental disorders.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

References

- Besag F, Gobbi G, Aldenkamp A, Caplan R, Dunn DW, Sillanpää M. Psychiatric and behavioural disorders in children with epilepsy (ILAE task force report): behavioural and psychiatric disorders associated with childhood epilepsy syndromes. *Epileptic Disord* 2016;18(Suppl. 1):S37–48.
- Vannest J, Tenney JR, Gelineau-Morel R, Maloney T, Glauser TA. Cognitive and behavioural outcomes in benign childhood epilepsy with centrotemporal spikes. *Epilepsy Behav* 2015;45:85–91.
- Strug LJ, Clarke T, Chiang T, Chien M, Baskut Z, Li W, et al. Centrotemporal sharp wave EEG trait in rolandic epilepsy maps to elongator protein complex 4 (ELP4). *Eur J Hum Genet* 2009;17:1171–81.
- Bethlehem RAI, Romero-García R, Mak E, Bullmore ET, Baron-Cohen S. Structural covariance networks in children with autism or ADHD. *Cereb Cortex* 2017;27:4267–76.
- Kanner AM, Scharfman H, Jette N, Anagnostou E, Bernard C, Camfield C, et al. Epilepsy as a network disorder (1): what can we learn from other network disorders such as autistic spectrum disorder and mood disorders? *Epilepsy Behav* 2017;77:106–13.
- Parisi P, Paulino MC, Raucci U, Ferretti A, Villa MP, Trenite DK. "Atypical forms" of benign epilepsy with centrotemporal spikes (BECTS): how to diagnose and guide these children. A practical/scientific approach. *Epilepsy Behav* 2017;75:165–9.
- Matsuo M, Maeda T, Sasaki K, Ishii K, Hamasaki Y. Frequent association of autism spectrum disorder in patients with childhood onset epilepsy. *Brain Dev* 2010;32:759–63.
- Clarke DF, Roberts W, Daraksan M, Dupuis A, McCabe J, Wood H, et al. The prevalence of autistic spectrum disorder in children surveyed in a tertiary care epilepsy clinic. *Epilepsia* 2005;46:1970–7.
- Steffenburg S, Steffenburg U, Gillberg C. Autism spectrum disorder in children with active epilepsy and learning disability: comorbidity, pre- and perinatal background and seizure characteristics. *Dev Med Child Neurol* 2003;45:724–30.
- Kavros PM, Clarke T, Strug LJ, Halperin JM, Dorta NJ, Pal DK. Attention impairment in rolandic epilepsy: systematic review. *Epilepsia* 2008;49:1570–80.
- Kim EH, Yum MS, Kim HW, Ko TS. Attention-deficit/hyperactivity disorder and attention impairment in children with benign childhood epilepsy with centrotemporal spikes. *Epilepsy Behav* 2014;37:54–8.
- Danhofer P, Pejčochová J, Dušek L, Rektor I, Ošlejšková H. The influence of EEG-detected nocturnal centrotemporal discharges on the expression of core symptoms of ADHD in children with benign childhood epilepsy with centrotemporal spikes (BCECTS): a prospective study in a tertiary referral center. *Epilepsy Behav* 2018;79:75–81.
- Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;30:389–99.
- Berument K, Rutter M, Lord C, Pickles A, Bailey A. Autism screening questionnaire: diagnostic validity. *Br J Psychiatry* 1999;173:444–51.
- Avçil S, Baykara B, Baydur H, Münir KM, İnal Emiroğlu N. The validity and reliability of the social communication questionnaire – Turkish form in autistics aged 4–18 years. *Turk Psikiyatri Derg* 2015;26(1):56–64.
- Öner P, Öner Ö, Çöp E, Munir KM. Reliability and validity of the Turkish version of the social communication scale. *Klinik Psikofarmakol Bulteni* 2012;22:43–50.
- Turgay A. Disruptive behavior disorders child and adolescent screening and rating scales for children, adolescents, parents and teachers. West Bloomfield, MI: Integrative therapy institute publication; 1994.
- Ercan ES, Amado S, Somer O. Development of a test battery for the assessment of attention deficit hyperactivity disorder. *Turk J Child Adolesc Ment Health* 2001;8:132–44.
- Markram H, Rinaldi T, Markram K. The intense world syndrome – an alternative hypothesis for autism. *Front Neurosci* 2007;1(1):77–96.
- Lai MC, Lombardo MV, Baron-Cohen S. Autism. *Lancet* 2014;383(9920):896–910.
- Lemke JR, Lal D, Reinthaler EM, Steiner I, Nothnagel M, Alber M, et al. Mutations in GRIN2A cause idiopathic focal epilepsy with rolandic spikes. *Nat Genet* 2013;45:1067–72.
- Lesca G, Rudolf G, Labalme A, Hirsch E, Arzimanoglou A, Genton P, et al. Epileptic encephalopathies of the Landau-Kleffner and continuous spike and waves during slow-wave sleep types: genomic dissection makes the link with autism. *Epilepsia* 2012;53:1526–38.
- Idring S, Rai D, Dal H, Dalman C, Sturm H, Zander E, et al. Autism spectrum disorders in the Stockholm youth cohort: design, prevalence and validity. *PLoS One* 2012;7:e41280.
- Blumberg SJ, Bramlett MD, Kogan MD, Schieve LA, Jones JR, Lu MC. Changes in prevalence of parent-reported autism spectrum disorder in school-aged US children: 2007 to 2011–2012. Hyattsville, MD: National Center for Health Statistics; 2013.
- Russell G, Rodgers LR, Ukoumunne OC, Ford T. Prevalence of parent-reported ASD and ADHD in the UK: findings from the millennium cohort study. *J Autism Dev Disord* 2014;44(1):31–40.
- Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marcini C, et al. Global prevalence of autism and other pervasive developmental disorders. *Autism Res* 2012;5:160–79.
- Filippini M, Boni A, Giannotta M, Gobbi G. Neuropsychological development in children belonging to BECTS spectrum: long-term effect of epileptiform activity. *Epilepsy Behav* 2013;28:504–11.
- Barkley RA. Attention-deficit hyperactivity disorder: a handbook for diagnosis and treatment. 3rd ed. New York: The Guilford Press; 2006.
- Long Z, Duan X, Chen HH, Zhang Y, Chen HH. Structural covariance model reveals dynamic reconfiguration of triple networks in autism spectrum disorder. *Appl Informatics* 2016;3:7.
- Carotenuto M, Parisi P, Esposito M, Cortese S, Elia M. Sleep alterations in children with refractory epileptic encephalopathies: a polysomnographic study. *Epilepsy Behav* 2014;35:50–3.
- Parisi P, Bruni O, Pia Villa M, Verrotti A, Miano S, Luchetti A, et al. The relationship between sleep and epilepsy: the effect on cognitive functioning in children. *Dev Med Child Neurol* 2010;52:805–10.
- Parisi P, Moavero R, Verrotti A, Curatolo P. Attention deficit hyperactivity disorder in children with epilepsy. *Brain Dev* 2010;32:10–6.