SciMedCentral

Journal of Sleep Medicine & Disorders

Short Communication

Sleep Disorders and Attention Deficit/Hyperactivity Disorder in Children and Adolescents Presenting Genetic Epilepsies with Typical Absence Seizures: An Observational Study

Maddalena Duca[1,2]*, Benjamin Putois[2], Joseph Toulouse[2], Isabella Cocco[2], Carlo Cottone[1], Antonia Parmeggiani[1], Emilio Franzoni[1], Julitta De Bellescize[2], Eleni Panagiotakaki[2], Vania Herbillon[2], Faustine Ilski-Lecoanet[2], Alexis Arzimanoglou[2], and Patricia Franco[2]

[1]UO Neuropsichiatria Infantile, Azienda Ospedaliero Universitaria Policlinico S. Orsola-Malpighi, Bologna

[2]Department of Pediatric Clinical Epileptology, Sleep Disorders and Functional Neurology, University Hospitals of Lyon, France

***Corresponding author**

Maddalena Duca, UO Neuropsichiatria Infantile, Azienda Ospedaliero Universitaria Policlinico S. Orsola-Malpighi, Bologna, France, Tel: 0039335220143; Email: Maddalenaduca@hotmail.it

Submitted: 25 February 2018

Accepted: 19 March 2018

Published: 21 March 2018

ISSN: 2379-0822

Keywords

- Children
- Epilepsy with absence
- Sleep
- ADHD
- Antiepileptic drugs

Abstract

This study investigated sleep disorders (SD) and Attention Deficit/Hyperactivity Disorder (ADHD) symptoms in children with absence epilepsy (AE). Parents completed questionnaires on sleep disturbance, Anti-Epileptic Drugs (AED) side effects, and ADHD symptoms. Seventy children with absence seizures included in this study have been compared to a healthy sample matched on sex, age and body mass index. In the AE group, 59% were controlled by AED, 25% had ADHD clinical diagnosis, 15% had AED adverse effects. Considering the whole epileptic group, 17% had pathological scores on ADHD Rating scale and 21% reported excessive daytime sleepiness. Inattention, excessive somnolence and sleep breathing disturbance have been more frequently found in children with AE than in healthy controls. The children with AED adverse effects had higher ADHD scorers and more complaints of excessive daytime sleepiness. This study incites to control for SD and ADHD before and after AED treatment in AE children.

ABBREVIATIONS

AE: Absence Epilepsy; ADHD: Attention Deficit/Hyperactivity Disorder; AED: Anti-Epileptic Drugs; BMI: Body Mass Index; SD: Sleep Disorders; SDSC: Sleep Disturbance Scale for Children

INTRODUCTION

Sleep disorder and epilepsy are very common conditions in children and their comorbidity and mutual influence has been observed [1]; the presence of both of these conditions lead to a worse quality of life and it could interfere with the control of seizures [2]. In literature many authors attributed sleep structure alterations to epileptic activities [3,4]. The most reported disturbances are longer sleep onset latency, increased frequency and duration of awakenings after sleep, shorter sleep time and lower sleep efficiency, reduced or abnormal K complexes and sleep spindles, reduced or instability of REM sleep and increased stage shifts [3].

In literature, it is known that sleep pathologies and some epileptic seizures can be associated with Attention Deficit/Hyperactivity Disorder (ADHD). Absence seizures are brief (4-20 s) and frequent (ten per days) epileptic attacks with abrupt and severe loss of consciousness. The ictal EEG show generalized discharges of high-amplitude spike at around 3 Hz with gradual and regular slowdown. The seizures appear during wakefulness in children with normal neurological examination and development.

Children presenting absence epilepsy (AE) seem inattentive if the seizures are not controlled by treatment; therefore it's important to evaluate the presence of sleep disorders and epileptics seizures in children with ADHD [5]. Similarly, some authors reported that a child presenting epilepsy at the disease onset and ADHD symptoms should be carefully examined before the beginning of the treatment, in order to obtain a better therapeutic management of the double symptomatology. A correct identification and treatment of the common sleep disorders could represent an essential component of the analysis and management of these patients [6].

Several studies on sleep disorders in children with epilepsy used parent questionnaires. Stores et al. showed a lower sleep quality and a higher anxiety regarding sleep in 79 children presenting epilepsy compared with a control group [7]. Other authors have utilized the Sleep Behavior Questionnaire (SBQ), an instrument that presents a total score and different items on sleep onset latency difficulties, parent-child interaction during the night, sleep fragmentation, parasomnia and diurnal sleepiness. Patients with epilepsy had more sleep difficulties than controls [8,9].

In literature, to our knowledge, there are no systematic studies of ADHD and SD in AE. The objective of this study is to investigate the presence of SD and ADHD symptoms in children presenting AE, and thus to improve the management of these children.

MATERIALS AND METHODS

This study is an observational survey. It has been conducted during an internship at the service Epilepsie, Sommeilet Exploration Fonctionelles Neuropédiatriques, Femme-Mère-Enfant Hospital, Lyon, France, and continued at the Complex Unit of Infantile Neuropsychiatry, S. Orsola Malpighi Hospital, Bologna, Italia, in a period between October 2015 and July 2016. The inclusion criteria of the study were: 5 -16 year-old children with confirmed diagnosis of AE according to International League against Epilepsy classification [5]; normal neurological examination. Our protocol has been approved by ethics committee of Femme-Mère-Enfant Hospital. All parents signed a parental consent form.

The parents of the patients presenting AE completed the Sleep Disturbance Sleep for Children (SDSC) divided in 5 subscales (difficulty in initiating and maintaining sleep, sleep breathing disorders, disorders of excessive somnolence, parasomnias and non-restorative sleep) [10-12], and the ADHD rating scale divided in inattention and hyperactivity subscales [13]. They also answered the questions about the adverse effects of antiepileptic drugs (AED) during the last four weeks before the last clinical examination slowing down of thought, memory difficulty, confusion, impaired schoolchildren results, reduced concentration, instability, altered coordination, falls, change of personality, vertigo, headache, increase or loss of appetite, increase or loss of weight. These questions have been asked systematically during the medical examination and in some cases the questionnaires have been sent to patients' home by postal service.

Anamnestic data about epilepsy features and therapy were collected at the last examination and/or in the medical report.

The AE sample was matched with healthy children from the study on the French validation of the SDSC [12]. These children were matched with sex ratio, age and body mass index (BMI). The control sample included 43 children. T-test were used to compare AE and healthy group. The statistical significance was considered for $p < .05$.

Spearman correlation between SDSC subscales, ADHD rating subscales and AED adverse effects were computed with Bonferroni correction (statistical significance was considered for $p < .0005$).

RESULTS

The AE sample was composed of 70 children, M: F ratio was 1:1. The epileptic syndromes were distributed as follows: 42 (60%) children reported Childhood Absence Epilepsy, 11(16%) Juvenile Absence Epilepsy, 9 (13%) Early Onset Absence Epilepsy, 6 (8%) with Eyelid Myoclonia with Absences and 2 (3%) with Myoclonic Absence Epilepsy. Ten children had manifested febrile seizures and 18 generalized tonic-clonic seizures during their history. The mean age of onset was 6 years and 4 months (range 9 months-12 years 11 months). The mean age at the last examination was 10 years and 4 months (5-16 years). All children received a pharmacological treatment. Fifty-nine % of the sample (41/70) did not present anymore seizures during the six months before the last examination (Table 1).

The most frequent side effects of the drugs were fatigue (n=12, 17%), reduced concentration (n=12, 17%), attention problems (n=11, 15%) and poor performance in school (n=7, 10%). In the AE children, the ADHD rating scale score was abnormal for inattention in 37%, for hyperactivity 26%, subtype mixed 23%. Despite the fact that 76% of parents did not report issues related to their children' sleep, only 57% of the questionnaires regarding these disorders had normal scores: in fact, 43% of the sample reported at least one pathological result. The main disorders, isolated or associated to other sleep problems were subdivided as follows: 21% excessive diurnal sleepiness, 14% breathing related sleep disorders, 11% insomnia, 7% parasomnia (sleep talking, bruxism, periodic limb movements during sleep), and 5% not restoring sleep.

Table 1: Epileptic characteristics of our AE sample.

Age at epilepsy onset (average/years)	6.4 (0.9-12.11)	
Seizures frequency in the last 6 months	**N**	**%**
0	41	59%
<5	19	27%
<10	4	6%
>10	6	8%
Generalized tonic-clonic seizures	18	26%
Pharmacological treatment distribution-		
Molecule		
VPA	29	41%
VPA+ETS	8	11%
VPA+LMT	8	11%
LMT	7	10%
ETS	5	7%
LEV	5	7%
VPA+LEV	3	4%
ETS+LEV	1	1%
LMT+CNZ	1	1%
VPA+AZM	1	1%
VPA+TPM	1	1%
ZNS	1	1%

Abbreviations: AZM: Acethazolamide; CNZ: Clonazepam; ESM: Ethosuximide; LEV: Levetiracetam; LTG: Lamotrigine; TPM: Topiramate; VPA: Valproic Acid; ZNS: Zonisamide

When we matched on sex ratio, age and body mass index (BMI), 43 children were included and were compared to 43 AE children. 27 AE children were not included in this analysis because they had not matched healthy children. T-test analysis revealed a significant statistical difference between epileptic and healthy children for the SDSC total score (43 versus 38; t=2.2, p=.003), excessive somnolence (4 versus 3; t=2.9, p=.003), sleep breathing disturbance (8,5 versus 7; t=2.3 p=.02), the ADHD rating scale total score (17 versus 11.8; t=2.54, p=.01) and ADHD inattention score (9.4 versus 6; t=2.82, p=.005). No significant differences were found for insomnia, parasomnia, non-restorative sleep and hyperactivity. Children presenting pathological excessive sleepiness were more frequently found in the AE group than in the healthy group (21% versus 5%; t=2.8, p=.006), the sleep breathing score have been considered in this analysis. There were marginally more epileptic children with pathological sleep breathing disturbance than healthy children (14% versus 6%; t=1.9, p=.06).

We have found a significant correlation between AED side effects and excessive somnolence (r=.43, p < 0.0005) and non-restorative sleep (r=.54, p < 0.0005) [14,15].

DISCUSSION

Inattention, excessive somnolence and sleep breathing disturbances were more frequently found in children with AE than for healthy controls. Children presenting epilepsy were more likely to have a sleep disorder. In literature, the impact of epilepsy on sleep has been evaluated in many studies [1,2]. Some authors have reported that its effect on sleep depends on the type of crisis [16] and others have affirmed that patients with Childhood Absence Epilepsy and Myoclonic Absence Epilepsy do not present sleep disorders [17]. Contrary to others, in this study, we found a significant difference between epileptic children and healthy controls for sleep disorders, especially for excessive somnolence, but not for insomnia and parasomnia; this last result could be explained by the fact that the severity of nocturnal epileptic seizures in AE is lower than in other forms of epilepsy.

One hypothesis could be that epilepsy itself could facilitate the development of excessive sleepiness in these patients. Indeed, some authors reported that epilepsy per se and/or seizures themselves promote sleep disruption and significantly affect both the quality, and the architecture of sleep [15] however these data are limited by the fact that it refers to the epilepsy more broadly and not to a specific type. Moreover, during sleep, the absence type spike wave discharges are associated with phasic arousals without awakening and could be implicated in the non-restorative effect of sleep in this disease [18].

Another hypothesis could be that the excessive somnolence is due to the secondary effects of drugs. Indeed, we found that AE children with AED side effects had more complaints on excessive daytime sleepiness. In literature, it was described that Valproic Acid and Ethosuximide could induce sleepiness with the increase of NREM1 [14] while Levetiracetam and Lamotrigine have less effect on sleep [15]. There are discrepancies in the results on the side effects of antiepileptic drugs on sleep [16]. In our study, 33% of the sample was treated with a bitherapy and this makes difficult to determine the impact of each drug on clinical outcome. The high heterogeneity regarding the dosage has also to be considered.

AE sample had more signs of respiratory disorders than the control sample even if they were matched on BMI. However, BMI could be as less accurate indicator than umbilical circumference to evaluate obesity [19]. At this point, we can hypothesis that the higher breathing disturbance score may be attributable to AE or AED [20]. 64% of the AE group received VPA that is known to induce an increase of weight. In another hand, respiratory disorders could induce hypoxia and facilitate excessive sleepiness and epileptic seizure. One limitation of this study is the absence of objective measure of Apnea-Hypopnea Index to confirm sleep breathing disorder (Table 2).

We have also found a significant correlation between AED side effects and ADHD (r=.51, p < 0.0005). The epilepsy children have a higher rate of ADHD symptoms, and these results could be associated with the AED side effects; moreover, these symptoms are also described as important predictors of SD in children [21]. In literature, it is reported that there are more ADHD symptoms in patients with AE treated with VPA rather than with ESM or LTG [22], however the VPA effect size in deficit attention was limited and many children probably had blood drug concentrations above the upper limit of the reference range [23]. A negative effect on behavior was also found in children treated with LEV [24]. These behavior side effects could also be related to sleep disturbances and excessive daytime sleepiness.

There are also several limitations in this study. First, it was difficult to quantify the pharmacological influence on behavior since the 33% of cases received a bitherapy with

Table 2: Age, BMI and sex matching comparison between AE and healthy children on ADHD rating scale and SDSC (* <.05).

	AE children	Control children
N	43	43
Age	8.4 (1.6)	8.8(1.5)
BMI	17.7 (3.1)	17.8 (3.6)
ADHD - Total score	16.9(10.2)	11.8 (8)*
ADHD - Inattention	9.3(6.4)	5.9(4.4)*
ADHD - Hyperactivity	7.5(5.2)	5.6(4.2)
SDSC Total score	43.4(10.9)	38.4(10.3)
SDSC - Insomnia	12.6 (5)	11.3 (3.8)
SDSC - Breathing disturbance	8.5(3.1)	7 (2.4)*
SDSC - Somnolence	4 (1.6)	3.2(0.6)*
SDSC - Parasomnia	12 (3.5)	11 (3.6)
SDSC - Non restorative sleep	5.9(2.6)	5.7(2.6)
Pathological AHDH	18.7% (39)	7% (26)
Pathological SDSC - Insomnia	11.7% (33)	47% (21)
Pathological SDSC - Breathing disturbance	21% (41)	7% (25)*
Pathological SDSC - Sleepiness	21% (41)	2,4% (15)*
Pathological SDSC - Parasomnia	9.4% (29)	7% (25)
Pathological SDSC - Non restorative sleep	7% (26)	7% (25)

a high heterogeneity regarding the dosage. Secondly, the sample compared to healthy children in our study is small (43 participants), however we carefully matched the control group with sex, age and body mass index. In the future, it would be important to consider a largest group to confirm our data.

CONCLUSION

The findings of this observational study show that there is most likely a link between the epilepsy with absence seizures and sleep disorder in children, especially in the presence of inattention, excessive somnolence and breathing disturbance during sleep. In everyday clinical practice we advise a methodic investigation of children with this type of epilepsy, using validated questionnaires on sleep disorders and the ADHD rating scale, as soon as possible at diagnosis of the epilepsy, before treatment. A systematic follow-up at 6 months, adding also an evaluation of AED adverse effects, would then allow early detection of eventual comorbidities and appropriate adjustment of the therapeutic strategies. Regarding the AED side effects and the clinical signs presented by children with absence seizures the parents' opinions play an important role according to the patient empowerment model [25].

REFERENCES

1. Manni R, Terzaghi M. Comorbidity between epilepsy and sleep disorders. Epilepsy Res. 2010; 90: 171-177.
2. Van Golde EG, Gutter T, de Weerd AW. Sleep disturbances in people with epilepsy; prevalence, impact and treatment. Sleep Med Rev. 2011; 15: 357-368.
3. Nunes ML, Ferri R, Arzimanoglou A, Curzi L, Appel CC, Costa da Costa J. Sleep Organization in Children With Partial Refractory Epilepsy. J Child Neurol. 2003; 18: 763-766.
4. Matos G, Andersen M, do Valle AC, Tufik S. The relationship between sleep and epilepsy: evidence from clinical trials and animal models. J Neurol Sci. 2010; 295: 1-7.
5. Selman JE. Attention Deficit-Hyperactivity Disorder. N Engl J Med. 2005; 352: 1607-1678.
6. Parisi P, Moavero R, Verrotti A, Curatolo P. Attention deficit hyperactivity disorder in children with epilepsy. Brain Dev. 2010; 32: 10-16.
7. Stores G, Wiggs L, Campling G. Sleep disorders and their relationship to psychological disturbance in children with epilepsy. Child Care Health Dev. 1998; 24: 5-19.
8. Batista BH, Nunes ML. Evaluation of sleep habits in children with epilepsy. Epilepsy Behav. 2007; 11: 60-64.
9. Wirrell E, Blakman M, Barlow K, Mah J, Hamiwka L. Sleep disturbances in children with epilepsy compared with their nearest-aged siblings. Dev Med Child Neurol. 2005; 47: 754-759.
10. 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.
11. Bruni O, Ottaviano S, Guidetti, Romoli M, Innocenzi M, Cortesi F, et al. The Sleep Disturbance Scale for Children. Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. J Sleep Res. 1996; 5: 251-261.
12. Putois B, Leslie W, Gustin MP, Challamel MJ, Raoux A, Guignard-Perret A, et al. The French sleep disturbance scale for children. Sleep Med. 2007; 32: 56-65.
13. DuPaul, GJ, Power TJ, Anastopoulos AD, Reid R. ADHD Rating Scale-IV: Checklists, norms, and clinical interpretation. New York: Guilford 1998. 2006.
14. Legros B, Brazil CW. Effects of antiepileptic drugs on sleep architecture: a pilot study. Sleep Med. 2003; 4: 51-55.
15. Kothare SV, Kaleyias J. Sleep and epilepsy in children and adolescents. Sleep Med. 2010; 11: 674-685.
16. Tinuper P, Bisulli F, Provini F, Geyer JD, Carney PR. Treating Epilepsy in the presence of sleep disorders. In: Pediatric Epilepsy 1st ed, 2013; 343-361. Mc Graw Hill.
17. Tassinari CA, Bureau M, Thomas P. Epilepsy with myoclonic absences. In: Roger J, Bureau M, Dravet C, Dreifuss F, Perret A, Wolf P (eds). Epileptic Syndromes in Infancy, Childhood and Adolescence, 2nd ed, 1992;151-160. London: John Libbey & Co.
18. Halász P, Terzano MG, Parrino L. Spike-wave discharge and the microstructure of sleep-wake continuum in idiopathic generalised epilepsy. Neurophysiol Clin. 2002; 32: 38-53.
19. Dobashi K. Evaluation of Obesity in School-Age Children. J Atheroscler Thromb. 2016; 23: 32-38.
20. Malow BA, Weatherwax KJ, Chervin RD, Hoban TF, Marzec ML, Martin C, et al. Identification and treatment of obstructive sleep apnea in adults and children with epilepsy: a prospective pilot study. Sleep Med. 2003; 4: 509-515.
21. Rheims S, Herbillon V, Villeneuve N, Auvin S, Napuri S, Cances C, et al. ADHD in childhood epilepsy: Clinical determinants of severity and of the response to methylphenidate. Epilepsia. 2016; 57: 1069-1077.
22. Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, et al. Ethosuximide, valproic acid and lamotrigine in childhood absence epilepsy. N Eng J Med. 2010; 362: 790-799.
23. Arzimanoglou A, Ryvlin P, Perucca E. When the past challenges the present: are older antiepileptic drugs still the best choice in childhood absence epilepsy. Lancet Neurol. 2010; 9: 457-459.
24. Aldenkamp A, Besag F, Gobbi G, Caplan R, Dunn DW, Sillanpää M. Psychiatric and Behavioural Disorders in Children with Epilepsy (ILAE Task Force Report): Adverse cognitive and behavioural effects of antiepileptic drugs in children. Epileptic Disord. 2016.
25. Ciccone MM, Aquilino A, Cortese F, Scicchitano P, Sassara M, Mola E, et al. Feasibility and effectiveness of a disease and care management model in the primary health care system for patients with heart failure and diabetes (Project Leonardo). Vasc Health Risk Manag. 2010; 6: 297-305.

Cite this article

Duca M, Putois B, Toulouse J, Cocco I, Cottone C, et al. (2018) Sleep Disorders and Attention Deficit/Hyperactivity Disorder in Children and Adolescents Presenting Genetic Epilepsies with Typical Absence Seizures: An Observational Study. J Sleep Med Disord 5(1): 1089.