ESCOLA DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO MEDICINA/PEDIATRIA E SAÚDEDA CRIANÇA
DOUTORADO EM MEDICINA/PEDIATRIA

FELIPE KALIL NETO

Avaliação da qualidade do sono em pacientes com Transtorno do Déficit de Atenção e Hiperatividade (TDAH) primário e TDAH como comorbidade da epilepsia

Porto Alegre
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Autor: Felipe Kalil Neto

Orientadora: Profa. Dra. Magda Lahorgue Nunes

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Tese apresentada como requisito para a obtenção do grau de Doutor pelo Programa de Pós-Graduação em Medicina/Pediatria e Saúde da Criança da Faculdade de Medicina da Pontifícia Universidade Católica do Rio Grande do Sul.

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Dedicatória

Admiração e companheirismo: dedico à minha Fernanda, meu grande amor, com quem construo minha vida e cultivo a arte de conviver

Amizade e fidelidade: dedico à minha Maria, companheira de todas as horas, e que me ensina o carinho mais puro

Vitórias e sucesso: dedico à meu pai, José Felipe, meu maior conselheiro e professor, com quem aprendi a sonhar e admirar

Coragem e perseverança: dedico à minha mãe, Cristina, que me ensinou a lutar, nunca desistir e desconhecer o impossível

Força e sensibilidade: dedico à minha irmã, Luísa, com a qual aprendi que firmeza, bondade e sinceridade são sinônimos e essenciais na vida.

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À Deus, independente de credo ou religião, pela proteção e força.

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À Ceres Oliveira, por toda a ajuda estatística e paciência.

Entre o sono e sonho,
Entre mim e o que em mim
É o quem eu me suponho
Corre um rio sem fim.

Passou por outras margens,
Diversas mais além,
Naquelas várias viagens
Que todo o rio tem.

Chegou onde hoje habito
A casa que hoje sou.
Passa, se eu me medito;
Se desperto, passou.

E quem me sinto e morre
No que me liga a mim
Dorme onde o rio corre —
Esse rio sem fim.

Fernando Pessoa

Mas quantas vezes a insônia é um dom. De repente acordar no meio da noite e ter essa coisa rara: solidão. Quase nenhum ruído. Só o das ondas do mar batendo na praia. E tomo café com gosto, toda sozinha no mundo. Ninguém me interrompe o nada. É um nada a um tempo vazio e rico. E o telefone mudo, sem aquele toque súbito que sobressalta. Depois vai amanhecendo. As nuvens se clareando sob um sol às vezes pálido como uma lua, às vezes de fogo puro. Vou ao terraço e sou talvez a primeira do dia a ver a espuma branca do mar. O mar é meu, o sol é meu, a terra é minha. E sinto-me feliz por nada, por tudo. Até que, como o sol subindo, a casa vai acordando e há o reencontro com meus filhos sonolentos.

Clarice Lispector

RESUMO

Objetivo: Sabe-se que tanto a epilepsia quanto o Transtorno do déficit de atenção e hiperatividade (TDAH) podem influenciar a organização do sono de diferentes maneiras. O objetivo deste estudo é avaliar a qualidade do sono em crianças e adolescentes com TDAH e epilepsia e analisar a influência do metilfenidato sobre a organização do sono.

Métodos: Estudo transversal, observacional, em crianças e adolescentes com epilepsia, sem crises por pelo menos 3 meses, e com TDAH, selecionados dos ambulatórios de epilepsia e neurologia infantil de um hospital terciário no Brasil. Os pacientes foram divididos em 4 diferentes grupos, cada um com 21 indivíduos: TDAH como comorbidade de epilepsia em uso de metilfenidato; TDAH como comorbidade de epilepsia sem uso do metilfenidato; TDAH e grupo controle. Todos os participantes foram avaliados pela Escala de Distúrbios de Sono em Crianças e monitorados por actigrafia durante 5 noites.

Resultados: A análise da actigrafia demonstrou maior número de despertares noturnos para os grupos epilepsia/TDAH, mais proeminentes no grupo sem metilfenidato ($p = 0,001$). Os relatos dos pais/cuidadores evidenciaram um maior risco de distúrbios do sono nos grupos epilepsia/TDAH sem metilfenidato e TDAH ($p < 0,001$).

Conclusão: O TDAH primário ou TDAH como comorbidade de epilepsia prejudicam a organização do sono em crianças. O uso de metilfenidato parece melhorar a qualidade do sono.

Palavras-chave: sono, epilepsia, TDAH, crianças, adolescentes

ABSTRACT

Objective/Background: Either epilepsy or attention deficit hyperactivity disorder (ADHD) can influence in different ways sleep organization. The aim of this study is to evaluate quality of sleep in children and adolescents with ADHD and epilepsy and to analyze the influence of methylphenidate on sleep organization.

Methods: This is an observational, cross sectional study, with children and adolescents with epilepsy, seizure free for at least 3 months, and with ADHD, selected from the epilepsy and child neurology outpatient clinic of a tertiary hospital in Brazil. Patients were divided into four different groups with 21 patients each: ADHD as comorbidity of epilepsy using methylphenidate; ADHD as comorbidity of epilepsy not using methylphenidate; only ADHD and a health control group. All participants were evaluated with the Sleep Disturbance Scale for Children and monitored with actigraphy for five nights.

Results: Actigraphic analysis showed a higher number of night awakenings at the epilepsy/ADHD groups, most prominent at the group without methylphenidate ($p=0,001$). Parental reports demonstrated a higher risk for sleep disturbances at the epilepsy/ADHD without methylphenidate and ADHD groups ($p<0,001$).

Conclusion: Primary ADHD or ADHD as a comorbidity of epilepsy impairs sleep organization in children. The use of methylphenidate seems to improve sleep quality.

Keywords: sleep, epilepsy, ADHD, children, adolescents

LISTA DE ABREVIATURAS

ADHD	Attention deficit hyperactivity disorder
AED	Antiepileptic drugs
ASDA	American sleep disorders association
BECTS	Epilepsia benigna da infância com descargas centro-temporais Benign epilepsy with centro-temporal spikes
BMI	Body mass index
CAP	Cyclic alternating pattern
DA	Disorders of arousal
DD	Distúrbios do despertar
DIMS	Distúrbios de início e manutenção do sono , Disorders of initiating and maintaining sleep
DRS	Distúrbios respiratórios do sono
DS	Distúrbios do sono
DSM V	Diagnostic and Statistical Manual of Mental Disorders
DTSV	Distúrbios da transição sono-vigília
EEG	Eletroencefalograma Eletroencephalogram
ESES	Electrical Status Epilepticus during slow-wave Sleep
FAE	Fármacos antiepilépticos
HS	Hiperidrose do sono
IED	Interictal epileptic discharges
InsCer	Instituto do Cérebro Brain Institute
MEI	Myoclonic epilepsy in infancy

MPH	Methylphenidate
MSLT	Multiple sleep latency test
PLMD	Periodic limb movement disorders
PUCRS	Pontifícia Universidade Católica do Rio Grande do Sul
RLS	Restless leg syndrome
SDB	Sleep breathing disorders
SDSC	Sleep Disturbance Scale for Children
SHY	Sleep hyperhydrosis
SRE	Sleep related epilepsy
SWI	Spike-wave index
SWTD	Sleep-wake transition disorders
TDAH	Transtorno do Déficit de Atenção e Hiperatividade
TST	Total sleep time

SUMÁRIO

CAPÍTULO I

1.1 INTRODUÇÃO

A qualidade do sono nas crianças e adolescentes tem sido um dos assuntos mais abordados pela comunidade científica. Sabe-se que um grande número de patologias pode levar a alterações na arquitetura do sono. Dentre estas, as epilepsias e o Transtorno do Déficit de Atenção e Hiperatividade (TDAH) encontram-se entre as patologias mais prevalentes[1,2,3].

Sabe-se que nas epilepsias podem ocorrer alterações nos ritmos circadianos que atuam sobre o hipotálamo, levando a mudanças na excitabilidade cortical e, consequentemente, na expressão das crises epilépticas[4,5]. Diante disso, os padrões de crises são afetados pelos ciclos do sono e vice-versa[6].

No que se refere ao TDAH, 55 a 74% dos pais relatam alterações na qualidade do sono de seus filhos[3,7,8,9,10]. Os mecanismos pelos quais os pacientes com TDAH apresentam distúrbios do sono ainda não estão claros e parecem ser multifatoriais[11]. Entre as queixas mais frequentes encontram-se a demora no início do sono e a manutenção do sono [8,11,12].

Tendo em vista o elevado percentual de pacientes com epilepsia que apresentam TDAH como comorbidade, torna-se necessário definir de forma clara a qualidade do sono destes pacientes. Em linhas gerais, sabe-se que estes pacientes apresentam alterações no sono [1,3,13,14]; entretanto, na literatura não encontram-se estudos relevantes que tenham avaliado de forma sistemática características do sono em pacientes portadores de epilepsia e que tenham como comorbidade o TDAH.

1.1.1 Sono

Distúrbios do sono (DS) são muito comuns na população pediátrica. A evolução e maturação do sono são dois dos processos mais marcantes na infância. Com isso, a qualidade do sono de uma criança influencia o desempenho diurno desta, tanto no ambiente familiar quanto escolar [15]. A conversa com os pais e uma anamnese adequada são elementos capazes de tranquilizar e demonstrar a benignidade do quadro na maioria das vezes [16].

Diversos estudos têm demonstrado que os DS na infância estão relacionados a limitações neurocognitivas [17]. Diante disso, entre as patologias mais estudadas no que se refere à qualidade e construção do sono estão o Transtorno de Déficit de Atenção e Hiperatividade (TDAH)[1] e as epilepsias[2].

Uma variedade de parâmetros funcionais caracteriza a fisiologia do sono. Durante o sono REM, ocorre um aumento da atividade de algumas estruturas do tronco, levando a uma variabilidade da homeostase de funções autonômicas, fato este que pode causar arritmias, frequência respiratória irregular e aumento do fluxo cerebral. Já no sono NREM (sono tranquilo), por outro lado, o cérebro assume um estado de baixa energia, com predomínio das atividades parassimpáticas, redução da frequência respiratória, da pressão arterial, da atividade do tronco cerebral e reduzida atividade muscular e hormonal, assim como do fluxo cerebral [18].

1.1.1.1 Macroestrutura do sono

A distribuição e magnitude dos parâmetros do sono refletem sua macroestrutura, a qual pode ser afetada por fatores endógenos e exógenos [19]. Ao avaliar a macroestrutura do sono os seguintes parâmetros são analisados: [2,19]

- Tempo total na cama;
    - Período total de sono;
    - Tempo total de sono: exclui-se os despertares;

- Latência de sono: tempo entre o apagar das luzes e o início do sono;
- Latência REM: tempo entre o início do sono e a primeira época de sono REM;
- Número de despertares/hora;
- Número de trocas de estágios/hora;
- Eficiência do sono: percentagem entre o tempo total de sono e o tempo na cama;
- WASO%: percentagem de período total de sono em vigília após o início do sono (tempo gasto acordado entre o início do sono e o final);
- Percentagem do período total de sono nos estágios 1,2, sono de ondas lentas e sono REM.

Sabe-se que pacientes com epilepsia frequentemente apresentam alterações na macroestrutura do sono, sendo este fato refletido na redução da eficiência do sono, aumento do número e da duração dos despertares noturnos, assim como o aumento da latência de início do sono e fragmentação do sono REM [20].

Em relação ao TDAH, as crianças apresentam um comprometimento significativo do sono quando são analisadas tanto medidas subjetivas (questionários) quanto objetivas (polissonografia ou actigrafia) [1,3].

1.1.1.2 Microestrutura do sono

Através da combinação de fatores homeostáticos e do ritmo circadiano, uma vez que o sono NREM tenha iniciado, ocorre uma inibição progressiva do sistema despertar-vigília. Com isso, ocorre uma progressão para atividades mais lentas, ocorrendo um aumento dos ritmos oscilatórios (como as oscilações lentas) e, consequentemente, o surgimento das ondas lentas do sono NREM. Dentre as manifestações do ritmo lento, os complexos K (marcador do sono NREM) e as ondas delta são as mais importantes [19].

Além disso, o sono NREM também é caracterizado pela presença de outras oscilações muito lentas (menos de 1 Hz), as quais são chamadas de padrão

alternante cíclico, cuja sigla, em inglês, é CAP (cyclic alternating pattern)[19]. O CAP é considerado um marcador fisiológico da instabilidade do sono NREM [19], traduzindo através do eletroencefalograma a tentativa do cérebro de preservar o sono mesmo em condições desfavoráveis (endógenas ou exógenas) [21].

1.1.1.3 Técnicas de investigação do sono

A polissonografia é o exame mais utilizado para estudo do sono e, por essa razão, é considerado o "padrão ouro" para a análise da arquitetura do sono e na detecção de distúrbios do sono. No entanto, apresenta limitações como técnica de investigação do sono: geralmente fornece apenas 1-2 noites de informações sobre o sono da criança; um número insuficiente de laboratórios de sono estão preparados para testar crianças; alto custo financeiro [22]. Nas duas últimas décadas, contudo, a actigrafia vem ganhando espaço como instrumento para pesquisa do sono [23,24,25].

A actigrafia é um método que usa um aparelho de pulso computadorizado semelhante a um relógio, que monitora e coleta dados gerados pelos movimentos [24]. Entre suas principais vantagens, estão: permitir ao paciente a monitorização em seu domicílio, ser custo-efetivo e apresentar concordância com relatos subjetivos do sono [24].

Tais características refletem-se, atualmente, na ampliação do número de publicações que abordam a actigrafia, bem como a inclusão desse método como instrumento válido para análise de pesquisa e medicina do sono [26], pela American Sleep Disorders Association (ASDA).

Conforme a revisão de Sadeh et al [26], a actigrafia:

- É válida e segura, se comparada à polissonografia, para analisar os padrões do sono em indivíduos normais;
- É um método custo-eficaz e objetivo para estudar os distúrbios do sono;
- É sensível na detecção de alterações nos padrões do sono e para análise de alterações no sono por intervenções farmacológicas e não farmacológicas;

- Apresenta adequada concordância, em sua maioria, com relatos subjetivos do sono;
- É um instrumento que, em última análise, afere movimentos e não o sono *per se*. Desta forma, é afetado por outros sistemas neurocomportamentais e mecanismos de controle não relacionados ao sono (ex.: distúrbios do movimento);
- Deve ser analisada em conjunto a métodos subjetivos e objetivos, de modo a afastar limitações resultantes do fato de os dados serem obtidos somente por movimentos corporais;
- Tem como limitação o fato de diferentes instrumentos serem designados a diferentes patologias;
- Quando realizada por um período de cinco ou mais dias, reduz a chance de erros de análise e aumenta sua confiança.

1.1.2 TDAH

O Transtorno de Déficit de Atenção e Hiperatividade (TDAH) é uma síndrome neuropsiquiátrica comum, bastante estudada nos últimos 50 anos. Caracteriza-se por um padrão persistente de desatenção e/ou hiperatividade, mais severo e freqüente do que o observado nos indivíduos da mesma faixa etária [27]. Sua prevalência em crianças de idade escolar varia de 3,5% a 18% conforme o critério diagnóstico utilizado [28]. A prevalência em adolescentes, no nosso meio, foi estimada em 5,8% [29].

O diagnóstico do TDAH é eminentemente clínico e realizado com base em dados de escalas de classificação que analisam sintomas, comportamentos e características individuais que trazem prejuízos significativos no funcionamento dos indivíduos em ambientes diversos. Existe consenso de que não é necessário a utilização de qualquer método complementar para o diagnóstico do transtorno [30].

1.1.2.1 Alterações do sono e TDAH

Cerca de 25-50% das crianças e adolescentes com TDAH apresentam distúrbios do sono [12]. Dentre estes incluem-se despertares noturnos, atrasos das fases do sono, aumento da atividade noturna [11,31] e insônia [32,33]. Apesar de estudos recentes [1] indicarem a existência da associação entre problemas do sono, TDAH e ansiedade, essa relação ainda não é claramente explicada.

Ao comparar pacientes com desenvolvimento normal e pacientes com TDAH, Wiebe e colaboradores sugerem que tanto as dificuldades para iniciar quanto para manter o sono podem afetar ambos os grupos, porém através de mecanismos diferentes [34]. Hvolby e colaboradores analisaram, através de actígrafo, a qualidade de sono em pacientes com TDAH. Como resultado, observou-se um tempo de latência do sono dos pacientes com TDAH de 26,3 minutos, enquanto que os controles apresentaram um tempo de latência de 13,5 minutos [35]. Neste mesmo estudo, foi relatada uma discrepância entre a análise objetiva do sono e os relatos subjetivos dos pais, os quais superestimaram o tempo de latência do sono [35].

Em estudo retrospectivo, Crabtree et al analisou o sono de 97 crianças de 3 a 18 anos com diagnóstico de TDAH [36]. Em 36% dos pacientes que realizaram polissonografia foram demonstrados distúrbios de movimentos periódicos de membros, enquanto que nos 16 pacientes que foram avaliados por actigrafia foi observada uma grande variabilidade a cada noite em relação ao tempo total de sono e tempo de latência do sono.

Já em relação aos pais de pacientes com TDAH, 55%-74% referem queixas de alterações do sono em seus filhos[3]. Assim, uma avaliação e tratamento adequados de tais problemas podem vir a trazer melhora na qualidade de vida destes pacientes.

Com relação à qualidade do sono dos pacientes com TDAH, a maioria dos fenótipos apresenta um maior grau de excitação [37]. Crianças com TDAH apresentam um comprometimento significativo do sono quando são analisadas tanto medidas subjetivas (questionários) quanto objetivas (polissonografia ou actigrafia)[1,3]. Em metanálise recente[38] demonstrou-se, por meio do actígrafo, diferenças entre pacientes com TDAH que usam metilfenidato e os que usam placebo. Os usuários

de metilfenidato apresentaram uma diminuição importante na análise da atividade média e uma redução importante do tempo total de sono quando comparados ao placebo.

1.1.3 Epilepsia

Estimativas revelam que a epilepsia atinge cerca de 50 milhões de pessoas no mundo, com uma prevalência de 2,2 milhões somente nos EUA[39]. A maior incidência de epilepsia ocorre na infância [40], sendo que, na faixa etária pediátrica, afeta de 0,5 a 1% das crianças [41].

Sabe-se que na criança com epilepsia há geralmente um comprometimento de qualidade de vida, funções cognitivas e do sono [42,43].

Apesar da maioria dos pacientes com epilepsia conseguirem remissão ou controle completo de suas crises com o primeiro ou segundo esquema de fármacos antiepilépticos (FAE) em monoterapia[44], por volta de 40% necessitam de doses elevadas de FAE, após múltiplas tentativas de controle. Pacientes nos quais o uso racional de 2 esquemas de FAE não controlou as crises podem ser agrupados como tendo epilepsias de difícil controle.

Pacientes com epilepsias, principalmente as refratárias, apresentam geralmente prejuízos nas suas funções cognitivas que se repercutem nas suas habilidades acadêmicas e no funcionamento social [42,43,45,46].

O tratamento das comorbidades psiquiátricas destes pacientes influi no comportamento, na capacidade de autonomia e no desenvolvimento de habilidades educacionais ou mesmo ocupacionais, resultando em benefício considerável na qualidade de vida dos pacientes e dos seus cuidadores [47,48,49,50,51,52].

1.1.3.1 Alterações do sono e epilepsia

Cerca de um terço dos pacientes com epilepsia apresentam convulsões durante o sono [53]. Segundo Kotagal et al, isso é causado devido a uma interligação entre os estados fisiológico e patológico do sono com a epilepsia.

Há diversos mecanismos pelos quais pode-se explicar as relações entre sono e epileptogênese. Dentre estes, a sincronização neuronal no sono NREM (o que facilita a propagação de descargas) associada a uma diminuição dos mecanismos inibitórios e a dessincronização do sono REM (diminuindo a transmissão através do corpo caloso) [53,54,55].

É sabido que o sono pode ativar a ocorrência de crises epilépticas e de anormalidades no EEG [56]. Van Golde refere que durante o sono NREM as descargas são facilitadas (provavelmente pelo padrão sincronizado do EEG), enquanto ocorre uma supressão durante o sono REM, dificultando a propagação de tais descargas devido ao padrão dessincronizado. A ação do sono, em algumas síndromes epilépticas, é bem conhecida, como na epilepsia benigna com descargas centro-temporais (BECTS). É uma síndrome de curso benigno, na qual as crises ocorrem predominantemente durante o sono, logo após a criança dormir ou ao despertar [57,58,59]. Observam-se anormalidades na microarquitetura do sono, como redução na taxa do padrão alternante cíclico [60].

Além disso, há evidências de que a formação da memória e performances cognitivas estejam relacionadas a estágios do sono (como ondas lentas ou REM). Essa observação pode ser vista nos pacientes com epilepsia, onde a interação entre descargas e eventos sincronizados no EEG poderiam explicar o déficit cognitivo [61].

Também reconhece-se que a privação do sono pode ser responsável pela ativação da atividade epileptiforme; entretanto, ainda existe a discussão se isto ocorre devido a indução do sono ou pela excitabilidade neuronal [62,63].

O aumento de despertares, sonolência diurna, redução do sono total e a maior necessidade da presença dos pais na hora de dormir são características presentes nas crianças com epilepsia do ponto de vista comportamental [64,65]. Além disso, sabe-se também que as alterações comportamentais e do padrão de sono pode vir a afetar tanto as crianças como os pais [66]. A ansiedade e o medo de que seu filho tenha uma crise noturna é uma hipótese plausível para justificar a piora da qualidade do sono [67].

Sabe-se que a qualidade do sono expressa por maus hábitos no sono é diretamente relacionada com o controle das crises convulsivas; contudo, outros fatores tais como atraso do desenvolvimento, crises noturnas, uso de politerapia ou

crises convulsivas generalizadas também estão associadas a má qualidade do sono[13].

Apesar de os problemas no sono serem uns dos principais responsáveis por alterações comportamentais nos pacientes com epilepsia, este fato é frequentemente ignorado [68]. Dessa maneira, as crianças com epilepsias apresentam uma grande incidência de distúrbios do sono, principalmente em aspectos qualitativos, de macroestrutura e de padrão cíclico alternado [14,57,69,70,71].

1.1.3.2 Epilepsia e TDAH

O TDAH é a comorbidade psiquiátrica mais prevalente nos pacientes com epilepsia, principalmente nos casos refratários, onde sintomas podem estar presentes em até 60-70% dos pacientes [50]. Nos pacientes com epilepsias, a elevada prevalência dos sintomas de TDAH piora substancialmente o prognóstico psicossocial, principalmente quando se leva em conta a maior sobrecarga do cuidador [50].

Nos pacientes com epilepsias, o diagnóstico do TDAH pode ser muito difícil dependendo do grau de comprometimento cognitivo, do tipo de síndrome epiléptica e dos fatores relacionados a epilepsia [52,61,72,73,74,75].

Os fatores que prejudicam a avaliação e podem simular TDAH são as crises subclínicas (descargas epileptiformes generalizadas), crises de ausência, crises parciais complexas e os efeitos colaterais dos FAE. Estes fatores de confusão têm que ser analisados antes da decisão terapêutica e, nestes casos, idealmente, deveria se realizar uma avaliação neuropsicológica.

Quanto à etiologia do TDAH na epilepsia, a maior evidência de que os sintomas de déficit de atenção não sejam secundários aos fatores relacionados à epilepsia, está na presença de sintomas de déficits na atenção que precedem o início da doença epiléptica nos pacientes com epilepsia recém diagnosticada (criptogênica ou idiopática) [76,77]. Nestas epilepsias a prevalência de TDAH é pelo menos 2,5 vezes maior [72,78].

A precedência dos sintomas de TDAH em relação ao aparecimento das crises leva a crer na hipótese de patologias coincidentes [79] que possuem mecanismos fisiopatológicos diferentes, não relacionados as variáveis da epilepsia como crises, descargas epileptiformes e uso de FAE.

1.2 JUSTIFICATIVA

Estudos que demonstram a inter-relação entre a tríade sono/TDAH/epilepsia ainda são escassos. Sabe-se que a instabilidade de qualquer uma dessas patologias afeta negativamente a qualidade de sono, a qualidade de vida, a frequência de crises e descargas, além do desenvolvimento cognitivo e neurológico em crianças.

Uma compreensão formal e o esclarecimento dessas relações podem auxiliar na melhoria da suspeição, reconhecimento e monitorização dos sintomas.

Com isso, há questões que merecem uma abordagem científica através de um estudo observacional. A primeira é avaliar eventuais diferenças entre o sono de pacientes com TDAH “primário” e de pacientes com TDAH como comorbidade de epilepsia. A segunda questão-chave é a influência do metilfenidato na qualidade do sono dos pacientes com epilepsia e TDAH.

O presente estudo surgiu do questionamento para esclarecer a relação causa-efeito entre epilepsias, TDAH e sono.

1.3 OBJETIVOS

1.3.1 Objetivo primário

- Avaliar a qualidade do sono em pacientes com TDAH primário e TDAH como comorbidade da epilepsia.

1.3.2 Objetivo secundário

- Avaliar o impacto do uso de metilfenidato na qualidade do sono em pacientes com epilepsia e TDAH.

1.4 REFERÊNCIAS BIBLIOGRÁFICAS

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CAPÍTULO II

2.1 ARTIGO DE REVISÃO

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Review article

The relationship between epilepsy, sleep disorders, and attention deficit hyperactivity disorder (ADHD) in children: A review of the literature☆

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ABSTRACT

Objective: To analyze the relationship between epilepsy, sleep disorders, and attention deficit hyperactivity disorder (ADHD).
Bibliographic search: A literature search of the PubMed database was performed using the following key words: epilepsy, sleep, and ADHD. In total, 91 articles were located in PubMed, 34 were selected for abstract reading and twelve articles were reviewed, in which the main objectives were examine the relationship between epilepsy, sleep and ADHD from several perspectives, including epidemiology, effect of comorbidities on academic performance and the factors leading to diagnostic difficulties among these three disorders
Results: Among the main findings, there were difficulties to start and maintain sleep in patients with epilepsy and ADHD, reduction in sleep efficiency, decreased seizure threshold, as well as behavioral and cognitive deficits in both groups.
Conclusions: It is important to know which symptom is the predominant one. For this reason, children and adolescents with epilepsy, ADHD and sleep disorders need to be assessed carefully before initiating treatment. Our review concluded that there is an important link in this pathological triad.

1. Introduction

Quality of sleep habits in infants and adolescents has been one of the most studied subjects nowadays. It is known that a great number of pathologies can lead to sleep architecture alterations. Epilepsy and attention deficit hyperactivity disorder (ADHD) are included between the most prevalent diseases [1–3].

Epilepsy syndromes can cause circadian rhythm alterations that act at the hypothalamus, leading to cortical excitability changes, and then, consequently, in seizure expression [4,5]. Before that, seizure patterns can be affected by sleep cycles and vise versa [6].

ADHD is the most prevalent psychiatric comorbidity in epilepsy patients, especially in the refractory cases, when symptoms can achieve 70% of patients [7]. This high prevalence of ADHD symptoms worsens substantially the psychosocial prognosis [7].

Moreover in ADHD, 55–75% of parents report sleep quality changes at their children [8–10]. Diseases mechanisms which explain sleep disorders at ADHD patients remains unclear and seems to be multifactorial [11]. The most frequent complaints are longer sleep latency and sleep maintenance [8,11,12].

Nevertheless, there are contradictory findings that need a better explanation. For example, Holley et al. [13] objectively measured by actigraphy the sleep of children with epilepsy alongside that of healthy controls. They did not find any differences in sleep measures between both groups. However, significant deficits in cognitive functioning were demonstrated that were not explained by differences in sleep.

Because there are still controversies regarding epilepsy, ADHD and sleep triad it becomes relevant to realize this literature review. The main objective of this article was to perform a review to assess the relationship between epilepsy, sleep disorders and ADHD. We will cover clinical features, diagnosis, comorbidities, and treatments. The approach proposed in the present study might give additional evidence based information to support clinical decision.

1.1. Bibliographic search

Our review was carried out using a protocol based upon the PRISMA statements [14]. A literature search was performed between

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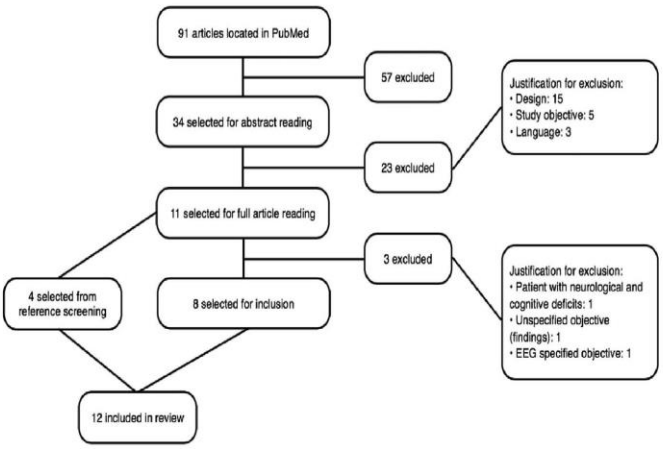

Fig. 1. Article selection and exclusion process.

the months of October and December 2015 from PubMed database. The key words used were: sleep AND epilepsy AND ADHD. Review articles were excluded, as well as editorials and case reports. We also excluded studies which the relation between sleep, ADHD and epilepsy were not adequately specified. The search totaled 91 articles in the PubMed database. Of these, 57 were excluded for not meeting the inclusion criteria, and 34 were considered relevant for this paper. 23 articles were excluded due to differences in study design (15), objective (5) and language (3). Of these, eleven were selected to be read as full texts. After, 3 articles were excluded secondary to unspecified findings (1), EEG specified objective (1) and inclusion of patients with neurological and cognitive deficits (1). Eight articles were considered relevant for this study [15–22].

The full reading and analysis of the studies also offered the possibility of access of other publications, which made it possible to include four new references in this review [23–26].

The process of search, selection and exclusion of articles in the literature is showed in Fig. 1.

1.2. Sleep×ADHD×Epilepsy: review of studies, interactions and cause-effect relationships

Epileptic patients often presents changes in sleep macrostructure, and this fact is reflected in the reduction of sleep efficiency, increase in number and duration of nocturnal awakenings, as well as increased sleep onset latency and the fragmentation of REM sleep [27]. As a major example, BECTS, a very well known benign epilepsy, in which attacks occur predominantly during sleep, after the child sleep or awakening [28–30].

Due to a number of descriptions of sleep related epileptic syndromes (ex.: autosomal dominant nocturnal frontal lobe epilepsy), the American Academy of Sleep Medicine created the term sleep related epilepsy (SRE), in order to designate those epilepsies in which more than 70% of seizures occur during sleep [31,32].

It is known that the quality of sleep expressed by bad habits during sleep is directly related to the control of seizures; however, other factors such as development delay, nocturnal crisis, polytherapy or generalized seizures are also associated to poor quality of sleep [33]. Patients with generalized and refractory epilepsy are more likely to have sleep abnormalities [34,35]. Although sleep problems are one of the main responsible for behavioral changes in patients with epilepsy, this fact is often ignored [36].

Wiebe et al. assessed the association between habitual sleep patterns and one night sleep polysomnography PSG with daytime sleepiness in ADHD patients and normal developing children. The authors analyzed eighty-two children (26 ADHD, 56 typically developing children) between 7 and 11 years. The patients had nighttime sleep recorded using actigraphy (habitual sleep patterns) over five nights and polysomnography (immediate sleep patterns) over one night. Daytime sleepiness was examined using the multiple sleep latency test (MSLT). Longer sleep latency (using both PSG and actygrapy) was related to longer mean sleep latencies in the MSLT in typically developing children. Time awake and night activity were positively related to MSLT in ADHD patients. The results showed that typically developing children and ADHD patients show a different relationship for habitual and immediate sleep patterns with daytime sleepiness. Moreover, their findings suggested that difficulties to initiate and to maintain sleep can be present in both nighttime and daytime sleep [23].

Hvolby and colleagues observed the quality of sleep in patients with ADHD through actigraphic and parental reports. A case-control study was designed, in which two hundred six children aged 5–11 years were analyzed. Fortyfive children with ADHD, 64 with other psychiatric diagnoses (psychiatric control group) and 97 healthy control subjects were selected. As a result, there was a longer sleep onset latency of patients with ADHD (26.3 min) and more irregular sleep pattern compared to the other two groups (psychiatric group had 18.3 min, while controls showed a shorter time of 13.5 min) [24]. The authors concluded that some children with ADHD have disturbed sleep that cannot be justified by comorbid oppositional defiant disorder. In the same study, a discrepancy was held between objective sleep analysis and subjective reporting of parents who overestimated the time of sleep latency [24].

On the other hand, Gruber et al., in a study using actigraphic monitoring over five consecutive nights and sleep diaries. The number of participants selected for the study was thirty-eight school-age boys with ADHD diagnosis and 64 control school-age boys. They observed an increased instability in sleep onset and duration in the ADHD group compared to controls. These findings support the idea that children with ADHD have a sleep-wake system instability [25].

In a retrospective study, Crabtree et al. examined the sleep of 97 children aged 3–18 years diagnosed with ADHD [26]. In 36% of patients who undergo polysomnography periodic limb movement disorders (PLMD) has been demonstrated, whereas in 16 patients who were evaluated by actigraphy was observed a large variability every

night on the total sleep time and sleep latency time. Between the major findings of this paper is a high prevalence of subjective sleep complaints among the parents of ADHD children, including difficulties to initiate and to maintain sleep, restless sleep and daytime sleepiness. Moreover, objective sleep analysis showed delayed sleep onset, increased nocturnal variability in sleep structure and pattern, and a high proportion of children with PLMD [26].

Furthermore, by analyzing the ADHD etiology in epilepsy, the greatest evidence that symptoms of attention deficit are not secondary to factors related to epilepsy, is the presence of symptoms of deficits in attention that precede the onset of epileptic disease in patients with newly diagnosed epilepsy (cryptogenic or idiopathic) [37,38]. These epilepsy prevalence of ADHD is at least 2.5 times higher [39,40].

The precedence of the symptoms of ADHD in relation to the onset of seizures suggests the possibility of matching conditions [41] that have different pathophysiological mechanisms, unrelated to the epilepsy variables such as seizures, epileptiform discharges and use of antiepileptic drugs (AED).

Wannag et al. [15] studied children with ADHD and nocturnal epileptiform activity admitted to a epilepsy Center. It was a prospective study of children aged 6–14 years. Among the 362 patients with epilepsy and normal intellectual functioning, 46 were referred with a probable diagnosis of ADHD. Of these, 43 were using AED and 30 had the diagnosis ADHD. Seven out of 30 ADHD patients presented focal nocturnal epileptiform activity (FNEA) on EEG. The proportion of children with ADHD in this study was higher than the rate reported in children with newly diagnosed seizures, but lower compared with rates from another tertiary centers. One of the main findings of this study demonstrated the occurrence of subclinical epileptiform activity during 24-h full EEG recording in children with ADHD and epilepsy.

In 2015 a retrospective study was conducted by Uliel-Sibony [16], seventeen patients with BECTS (3.5–10 years) were identified, and the spike-wave index (SWI) and learning disabilities were observed. All children had ADHD diagnosis and all patients were using AED. The follow-up range time was 1–10.5 years. Of these, 6 children were diagnosed with learning disabilities in addition to ADHD. One boy had only ADHD and behavioral difficulties. One patient had aggression and other patients had behavioral problems, which required psychiatric medications. Curiously, six patients had ADHD or speech difficulty diagnosis during preschool years, long before the diagnosis of epilepsy had been established. A behavioral deterioration was not detected in any of them. This study suggested that when treating a child with BECTS, high SWI (> 60%) and learning difficulties, the most important parameter for deciding whether to use a new AED is a formal psychological evaluation that proves cognitive decline. Other way, these medications must be avoided.

Continuing on the same subject, 196 patients (118 male and 78 female) with BECTS were evaluated and followed-up for a mean time of 4.4 years (range 2–11) [17]. All patients had their epilepsy diagnosis between 3 and 14 years of age. Seventy-eight patients experienced a generalized tonic-clonic seizure during the follow-up period. Levels of regression were evidenced by IQ decline in four children, ADHD in five, aggressive behavior in three and language deterioration in four children. Nine patients developed electrical status epilepticus in slow waves sleep (ESES). Sixty-one patients (31%) had ADHD, 43 (21.9%) had cognitive deficits and 23 (11.7%) had behavioral abnormalities. This study strengthened the high prevalence of ADHD between BECTS patients.

Cohen and colleagues [18] analyzed 186 children (109 males and 77 females) aged 2–18 years. Their parents were asked to apply the Sleep Disturbance Scale for Children (SDSC). The questionnaire were divided into three groups according to their major neurological diagnosis: epilepsy (58 patients), ADHD (62 patients), or others (66). Fifty children had an abnormal total sleep score. The most predominant sleep disorders reported were excessive somnolence (25.3%), initiating and maintaining sleep (24.7%) and arousal nightmares (23.1%). There was no significant group difference in prevalence of a pathological total sleep score or of any sleep abnormality. The only significant findings were that sleep-wake transition disorders (SWTD) was more frequent in children with epilepsy.

Comorbidities of attention deficit-hyperactivity disorder were evaluated by Ishii et al. [19]. The subjects consisted of 68 children and adolescents (nine preschool children aged 4–6 years, 50 elementary school children aged 7–12 years, nine adolescents aged 13–19 years; mean age: 9.7 years). Patients with mental age below age 4, and those with IQ under 50 were excluded, as well as those meeting criteria for pervasive developmental disorder. In 36 cases no comorbidity were recognized, although multiple comorbid disorders were noted in several cases. Among these, two cases had sleep disorders (parasomnias such as night terrors or sleepwalking) and five had the diagnosis of epilepsy (two non-febrile convulsion, one frontal lobe epilepsy and two not specified).

Another relevant question, is the relation between ADHD and electroencephalogram (EEG). Altunel [20] conducted a retrospective chart study of 134 patients who met the diagnostic criteria for combined ADHD. The main objective of this study was to elucidate the EEG abnormalities in ADHD. None of the patients had any other disease or behavioral manifestation other than ADHD. A total of 134 EEG were analyzed, and all patients presented spike and wave paroxysms that changes with age. 38 patients had a finding of benign focal epilepsy of childhood. Only half of the patients presented seizures and 46 patients had neither seizures nor foci. The authors concluded that spike and wave activity changes in time and that EEG discharges, even when a diagnosable epileptic disorder is absent, can be related to neuropsychiatric symptoms.

On a similar subject matter, an italian group [21] explored the prevalence of ictal and interictal epileptic discharges (IED) and sleep disorders in ADHD children. Forty-two ADHD patients (mean age 8.9 years) were included in this study. They were referred by psychiatry and pediatric neurologists to a sleep clinic. None of the ADHD patients showed intellectual deficit. 6% presented co-morbid Tic disorder, 12.8% dyspraxia, 33.3% learning disorders, 7.6% eating disorder and 12.8% language. A high prevalence (86%) of sleep disorders was reported. Among these, 26% has restless leg syndrome (RLS), 53.1% had IEDs, and three patients had nocturnal seizures. The general findings of this paper reinforce the fact that seizures/IEDs play an important role on cognitive and behavioral abilities, as well as ADHD is a condition frequently associated to EEG epileptiform abnormalities.

Another frequent syndrome in children is myoclonic epilepsy in infancy (MEI). Caraballo et al. [22] realized a follow-up of 38 patients with MEI. After a mean follow-up of 13.5 years, 32 patients had normal neurologic and neuropsychological evaluations. Four patients had significant learning difficulties (two of them with ADHD) and another two patients had important cognitive impairment, despite adequate seizure control (Table 1).

2. Discussion

The number of studies available in the literature specifying the relationship between sleep/ADHD/epilepsy still scarce. The combination of these three pathologies is a source of continuous clinical debate, as our review demonstrate. The necessity for a correct treatment raises the question about cause-consequence.

Attention deficit hyperactivity disorder (ADHD) is a common neuropsychiatric syndrome. It is characterized by a persistent lack of attention and hyperactivity pattern, more severe and frequently than observed in the same age group [42]. It's prevalence varies from 3.5% to 18% according to the diagnostic criteria utilized [43].

ADHD diagnosis is eminently based upon clinical symptoms and data scales (Ex: SNAP IV) that analyze individual characteristics which cause significant losses in the child's behavior in different environments. There is consensus that is not necessary the use of any complementary method for the diagnosis of ADHD [44].

Table 1
Studies reviewed, authors, age range , number of participants, main objective, findings, and outcomes.

Author/year of publication	Age range	n	Main objective	Findings	Conclusions
Wannag et al. [14], 2010	6–14 years	46	– Determine relationship between ADHD and quantity of focal nocturnal epileptiform activity (FNEA)	– FNEA present in 7/30 ADHD patients	– No possible causal effect of FNEA on ADHD
Ulhel-Sibony et al. [15], 2015	3–10 years	17	– Avoid aggressive therapies in BECTS, ESES and academic difficulties	– High SWI and ADHD prevalence	– Formal psychological evaluation is the most important parameter to use a new AED
Tovia et al. [16], 2011	3–14 years	196	– Delineate the frequency of atypical features of BECTS	– 61 had ADHD – 9 had ESES	– Prevalence of atypical forms of BECTS is low, but ADHD is high
Cohen et al. [17], 2013	2–18 years	186	– Detect sleep disturbances applying SDSC	– 50 children had abnormal sleep score	– Sleep disorders mechanisms may not be related to primary disease
Ishii et al. [18], 2003	4–19 years	68	– Comorbidity in ADHD	– 5 had epilepsy – 2 sleep disorders	– Multiple comorbid disorders in several cases
Altunel et al. [19], 2013	–	134	– EEG abnormalities	– 38 BECTS – All presented spike/ wave at some time	– EEG discharges are related to neuropsychiatric symptoms
Silvestri et al. [20], 2007	8,9 (mean Age)	42	– Prevalence of IED and seizures in ADHD children	– 86% sleep disorders – 53,1% had IEDs	– Seizures/IED have important role on cognitive abilities and ADHD
Caraballo et al. [21], 2013		38	– Analyze features, treatment and outcome of MEI	– 4 learning disabilities (two ADHD)	– Good outcome in terms of seizure control and neuropsychological profile
Hvolby et al. [23], 2008	5–11 years	206	– Actigraphic and parental reports of sleep difficulties in ADHD	– ADHD had longer sleep onset latency	– Discrepancy between objective sleep analysis and subjective reporting of parents
Gruber et al. [24], 2000	–	102	– Compare sleep-wake system of ADHD with controls	– Increased sleep onset and duration in ADHD	– Instability of sleep-wake system in children with ADHD
Crabtree et al. [25], 2003	3–18 years	97	– Sleep in ADHD with PSG	– 36% PLMD – Variability in total sleep time and latency	– High prevalence of subjective sleep complaints among parents of children with ADHD
Wiebe et al. [22], 2013	7–11 years	82	– Compare ADHD sleep/sleepiness to control		– Both groups can have difficulties to start and maintain sleep, by different mechanisms

About 25–50% of children and adolescents with ADHD show sleep disturbances [12]. Among these include nocturnal awakenings, delay of the sleep phases, increased nocturnal activity [11,25] and insomnia [45,46]. Children show significant commitment of sleep in both subjective (questionnaires) and objective (polysomnography or actigraphy) measures [1,3]. 55–74% of parents of ADHD patients refer sleep complaints in their child [3]. Therefore, an adequate evaluation and treatment can bring improvement in quality of life of these patients.

The highest incidence of epilepsy occurs in infancy [47], and it affects 0.5–1% of children [48]. It is known that children with epilepsy shows commitment in quality of life, cognitive function and sleep [49,50].

ADHD is the most prevalent psychiatric comorbidity in epileptic patients, mainly in the refractory cases, where symptoms can be presented in up to 60–70% of patients [7]. In patients with epilepsy, the high prevalence of symptoms of ADHD worsens substantially the psychosocial prognosis, mostly when taking into account the caregiver burden [7].

About a third of epileptic patients present seizures during sleep [51]. Sleep can activate the occurrence of seizures and electroencephalogram (EEG) abnormalities [52]. Van Golde refers that during NREM (non-rapid eye movement) sleep discharges are facilitated (most likely for the synchronized pattern of EEG), while a suppression occurs at REM (rapid eye movement) sleep, making it difficult the propagation of the discharges secondary to a desynchronized pattern [53,54].

The effect of sleep in some epileptic syndromes is well known, as in benign epilepsy with centro-temporal spikes (BECTS). It is also recognized that sleep deprivation can be responsible for epileptiform activity; however, it still exists the discussion if it occurs secondary to sleep induction or neuronal excitability [53,54].

Increase of awakenings, daytime sleepiness, reduced total sleep and the greatest need for the presence of parents at bedtime are important characteristics of children with epilepsy, from the behavioral point of view [55,56]. Moreover, it is also known that sleep patterns and behavior changes may come to affect both children and parents [57].

Anxiety and fear that the child have a night crisis is a plausible hypothesis to explain the worsening of sleep quality [58]. According to Parisi et al. this is reflected in the fact that children with epilepsy present better cognitive and behavioral prognosis when they have an adequate quality of sleep and seizure control [59].

Another important issue is to evaluate possible differences between the sleep of patients with "primary" ADHD and patients with ADHD as epilepsy comorbidity. The second key issue is the influence of methylphenidate on sleep quality of patients with epilepsy and ADHD. In a recent study [60], it was demonstrated by means of actigraph, differences among ADHD patients using methylphenidate and those using placebo. The methylphenidate users showed a significant decrease in the analysis of average activity and a significant reduction in total sleep time compared to placebo.

This fact leads us to another question: despite the effectiveness of methylphenidate, with improvement in approximately 70% of patients [61], and few side effects, a major impasse in daily clinical practice is the decision to treat epileptic patients or those with epileptiform EEG abnormalities [62]. Thus, the uncertainty of decreased threshold for seizures can interfere with medical management, depriving the patient receiving the drug which has the greatest efficacy on the symptoms it presents.

Our study exposes and reinforces the importance to know which symptom is the predominant one. Is it seizures? Is it inattention/hyperactivity? Sleep problems are a primary disorder or consequence of another pathology? For this reason, children and adolescents with epilepsy, ADHD and sleep disorders need to be assessed carefully before initiating treatment.

Conflicts of interest

The authors declare no conflict of interest.

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CAPÍTULO III

3.1 ARTIGO ORIGINAL

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Original Article

Evaluation of sleep organization in patients with attention deficit hyperactivity disorder (ADHD) and ADHD as a comorbidity of epilepsy

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ABSTRACT

Objective/background: Epilepsy or attention deficit hyperactivity disorder (ADHD) can influence sleep organization in different ways. The aim of this study was to evaluate sleep organization in children and adolescents with ADHD and epilepsy, and to analyze the influence of methylphenidate.
Methods: This was an observational, cross-sectional study of children and adolescents with epilepsy, who were seizure free for at least three months, and were also diagnosed with ADHD. They were selected from the epilepsy and child neurology outpatient clinic of a university hospital in Brazil. After sample size calculation, patients were consecutively included into four different groups, with 21 patients each: epilepsy + ADHD using methylphenidate, epilepsy + ADHD not using methylphenidate, only ADHD, and a healthy control group. All participants were evaluated with the Sleep Disturbance Scale for Children (SDSC) and monitored with actigraphy for five nights/days.
Results: Actigraphic analysis showed a higher number of night awakenings in the epilepsy + ADHD groups; they were most prominent in the group without methylphenidate ($p = 0.001$). Parental reports demonstrated a higher risk for sleep disturbances in the epilepsy + ADHD without methylphenidate and the ADHD groups ($p < 0.001$).
Conclusion: Primary ADHD as a comorbidity of epilepsy impairs sleep organization in children, and the use of short-acting methylphenidate seems to improve it. Both objective (actigraphic) and subjective (SDSC) measures showed significant sleep alterations between primary ADHD and ADHD as a comorbidity of epilepsy; this was most prominent in the group without methylphenidate.

1. Introduction

Recent studies have shown that inadequate sleep quality is reflected in negative aspects of neurodevelopment such as deterioration in school performance [1], obesity [2] and impulsiveness [3]. Several neurological disorders influence sleep organization and are often related to sleep complains, behavioral and cognitive alterations [1,2] (two of the most frequent being attention deficit hyperactivity disorder (ADHD) and epilepsy [4–8]).

It is known that patients with epilepsy may present with alterations in their circadian rhythms, which leads to changes in cortical excitability, and consequently the expression of seizures [9,10]. About a third of patients with epilepsy have seizures during sleep [11]. It is known that sleep can activate the occurrence of seizures and EEG abnormalities, and it is also recognized that sleep deprivation may be responsible for activation of epileptiform activity [12].

The association between sleep disorders and epilepsy has been previously reported, and its impact on quality of life is becoming increasingly recognized [8,13,14]. Children with epilepsy, even without refractory epilepsy or mental retardation, have an increased prevalence of sleep disorders, daytime sleepiness and sleep complaints when compared with controls [15,16].

Although there are contradictory findings in the literature, such as (the study of Holley et al. [17]), most of the available data show significant sleep alterations in patients with epilepsy and even more so in refractory cases [18].

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About 25–50% of children and adolescents with ADHD have sleep disorders [19], including nocturnal awakenings, phase delay, increased nighttime activity and insomnia [20]. Parents of children with ADHD frequently report sleep complaints [21]. Thus, proper evaluation and treatment of such problems are likely to bring improvement in the quality of life of these patients [22,23].

ADHD is the most prevalent psychiatric comorbidity in patients with epilepsy, especially in refractory cases where symptoms may be present in up to 60–70% of those affected [24]. In patients with epilepsy, the high prevalence of ADHD symptoms can substantially worsen the psychosocial prognosis, especially when taking into account the increased caregiver burden [24]. The diagnosis of ADHD in patients with epilepsy can be difficult, depending on the degree of cognitive impairment, the type of epilepsy syndrome, and the factors related to epilepsy [25,26].

The main objective of the present study was to evaluate sleep organization in patients with ADHD and patients with ADHD as a comorbidity of epilepsy. The second key issue was to analyze the influence of methylphenidate on sleep organization. It was hypothesized that patients with pure ADHD and ADHD as a comorbidity of epilepsy present with differences in sleep organization, and that methylphenidate has a positive influence on sleep organization of patients with epilepsy and ADHD. As the use of methylphenidate in patients with epilepsy is still a controversial issue, the approach proposed in the present study may provide additional evidence-based information to support this clinical decision.

2. Methods

This was an observational, cross-sectional study of volunteer patients, aged 7–18 years old, who were diagnosed with epilepsy and/or ADHD. They were followed in the outpatient Epilepsy and Child Neurology clinics of a university hospital in Porto Alegre, southern Brazil. Patients were consecutively enrolled in the study from September 2014 to April 2016, until the four groups were complete.

The sample size calculation for a 5% significance level estimated that each group should have 21 patients. According to their clinical condition, patients were consecutively included in one of the four study groups as follows: epilepsy + ADHD (using short-acting methylphenidate); epilepsy + ADHD without methylphenidate, ADHD using short-acting methylphenidate and a normal control group. In Brazil, the vast majority of patients from the public health system still make use of short-acting methylphenidate due to the high cost of long-acting formulations. Patients with epilepsy were seizure free for at least three months and using antiepileptic drugs as a monotherapy regimen. A control group with healthy children and adolescents without sleep complaints and any kind of medication was paired by age and sex with the epilepsy + ADHD (using methylphenidate) group.

Exclusion criteria for the epilepsy groups were: hearing and visual deficits, mild-to-severe cognitive deficits, refractory epilepsy, and using antiepileptic drugs as polytherapy. Exclusion criteria for the ADHD group were: using long-acting stimulants, diagnose of any other psychiatric disorders (anxiety, depression, oppositional defiant disorder) and use of any medication other than short-acting methylphenidate.

This study was approved by the Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS) ethics committee and review board. Parents and children signed written, informed consent.

The diagnosis of ADHD was confirmed by a child neurologist (FKN) using the following criteria: a standard neurological clinical history was taken (not specific to the study) from parents and children/adolescents, the SNAP IV scale by Swanson, Nolan and Pelham was completed by parents and teachers, the list of signs and symptoms from the *Diagnostic and Statistical Manual of Mental Disorders* (DSM V), and a medical evaluation of general health and neurological status [27,28]. As previously stated by Bechtel et al. [29], in order to avoid heterogeneity between ADHD groups (with some having ADHD due to seizure activity/epilepsy and others having "primary" ADHD), a careful clinical and developmental assessment was carried out by a child neurologist.

The diagnosis of epilepsy was achieved through clinical history, review of electroencephalograms (EEG) and neuroimaging. The patients that were selected were seizure free for at least three months, and using antiepileptic drugs as monotherapy. The frequency (classified according to the Engel scale) [30], and type (classified according to the International League Against Epilepsy-ILAE) [31] of seizures, as well as the medication dosages, onset of epilepsy and perinatal complications were evaluated during the clinical assessment with a child neurologist.

For evaluation of sleep disorders, a previously validated Brazilian Portuguese version of the Sleep Disturbance Scale for Children (SDSC) was applied [32,33]. The SDSC evaluates the six most common types of sleep disorders among children and adolescents: disorders of initiating and maintaining sleep, disorders of arousal, sleep-wake transition disorders, sleep hyperhidrosis, excessive somnolence, and sleep breathing disorders. This scale, which was answered by parents or caregivers, is composed of 26 questions, with scores from one to five for each question. When the scale score is 36–50, it is considered as risk; when ≥51, it is considered as a sleep disorder.

To analyze sleep organization, five-day actigraph monitoring was performed. Sleep organization was characterized through the analysis of total sleep time, sleep efficiency and sleep latency. Eleven actigraphs were used in this study: two from the Micro Motionlogger® (Ambulatory Monitoring, Inc., NY, USA) and nine from Act1 (EMSA Digital Actigraph, Rio de janeiro, Brazil). Patients were instructed to attach the actigraph to their nondominant wrists and to take it off their wrists only during bath time. A daily diary with information regarding awake and sleep time was used to complement the actigraphy.

Standard sleep parameters were observed: total sleep time (TST), total time in bed, sleep latency, sleep efficiency and number of awakenings after sleep onset. Total sleep time was measured as the total duration of sleep (epochs) between lights out and lights on, excluding night awakenings and sleep latency. Total time in bed was measured as the total duration of sleep (epochs) between lights out and lights on, including sleep latency and night awakenings. Sleep latency was calculated as the time (in minutes) from lights out to sleep onset. Sleep efficiency was calculated as the ratio of TST to the total time in bed. Number of awakenings was observed as three or more episodes of awakenings during more than five consecutive minutes. The actigraph algorithms showed an average of five nights of observation.

All of the evaluations were performed during the school year and included at least three week days.

2.1. Statistical analysis

The sample size calculation was based on the study by De Crescenzo et al. [34], and was conducted in PEPI version 4.0 (Programs for Epidemiologists). For an $\alpha = 0.05$ and 80% power ($\beta = 0.20$), it was estimated that it would take 21 patients per group to detect a standard deviation order in TST. The data were presented as mean and standard deviation and compared by analysis of variance (ANOVA), and complemented by the Tukey test. The Chi-squared test was used for categorical variables. To complement this test, the adjusted residuals test was applied, and the analysis of

Table 1
Socio-demographic profile and ADHD subtypes.

Variables	Epilepsy + ADHD without methylphenidate ($n = 21$)	ADHD with methylphenidate ($n = 21$)	Epilepsy + ADHD with methylphenidate ($n = 21$)	Control ($n = 21$)	p
Age (years), median ± SD	10.5 ± 3.3	10.4 ± 2.1	11.0 ± 2.6	10.9 ± 2.6	0.917[a]
Gender, n (%)					0.700[b]
Male	12 (57.1)	13 (61.9)	15 (71.4)	15 (71.4)	
Female	9 (42.9)	8 (38.1)	6 (28.6)	6 (28.8)	
Ethnicity, n (%)					0.575[b]
Caucasian	18 (85.7)	17 (81.0)	18 (85.7)	20 (95.2)	
Non-caucasian	3 (14.3)	4 (19.0)	3 (14.3)	1 (4.8)	
BMI, kg/m^2 mean ± SD	20.6 ± 4.6	20.0 ± 2.7	21.6 ± 5.6	21.9 ± 1.8	0.363[a]
ADHD subtype, n (%)					0.813[b]
Inattentive	16 (76.2)	14 (66.7)	16 (76.2)	–	
Hyperactive	0 (0.0)	1 (4.8)	1 (4.8)	–	
Combined	5 (23.8)	6 (28.6)	4 (19.0)	–	

SD, standard deviation; BMI, body mass index.
[a] One-way analysis of variance (ANOVA).
[b] Chi-square test.

Table 2
Characteristics of patients with epilepsy.

	Epilepsy/ADHD with methylphenidate	Epilepsy/ADHD without methylphenidate
[a]Focal epileptic seizure	$n = 10$ (48%)	$n = 11$ (52%)
[a]Generalized epileptic seizure	$n = 14$ (66%)	$n = 7$ (34%)
[a]Etiology	Unknown	Unknown
Medication	Carbamazepine ($n = 9$) Valproate ($n = 7$) Oxcarbazepine ($n = 4$) Sulthiame ($n = 1$)	Valproate ($n = 11$) Oxcarbazepine ($n = 5$) Carbamazepine ($n = 4$) Lamotrigine ($n = 1$)
[a]Epilepsy	Idiopathic focal epilepsy ($n = 13$) Generalized epilepsy ($n = 7$) BECTS ($n = 1$)	Generalized epilepsy ($n = 10$) Idiopathic focal epilepsy ($n = 8$) BECTS ($n = 2$) JME ($n = 1$)

BECTS: Benign Epilepsy with Centro-temporal Spikes; JME: Juvenile Myoclonic Epilepsy.
[a] Classification according to ILAE.

covariance (ANCOVA) was used to control confounding factors. In case of asymmetry, the Kruskal–Wallis test together with the Mann–Whitney test were applied.

3. Results

Clinical information regarding the 84 children and adolescents included in the study are shown in Table 1. There were no statistical differences in relation to age, sex, ethnicity, body mass index (BMI) and ADHD subtypes among the groups. The final sample included children and adolescents from families with educated and employed parents, belonging to middle and low socioeconomic classes, based on the family income, as classified by Brazilian Institute of Geography and Statistics (www.ibge.gov.br/home/estatistica/populacao/trabalhoerendimento/pnad98/saude/analise.shtm). Characteristics of the patients with epilepsy are described in Table 2.

The majority of patients with primary ADHD were of the inattention type (67%) followed by combined type (29%) and hyperactivity (4%). In the group epilepsy + ADHD with methylphenidate, the inattention type also predominated (76%) followed by the combined type (19%) and hyperactivity (5%); in the epilepsy + ADHD without methylphenidate group, 76% were from the inattention type and 24% of the combined type.

Table 3 summarizes the findings of sleep organization evaluated through actigraphic analysis. Among the variables studied, number of nocturnal awakenings was the only one that significantly differed between the groups.

Patients with epilepsy + ADHD without methylphenidate had a significant increase in the number of nighttime awakenings, both in relation to the controls and the primary ADHD group. The epilepsy + ADHD with methylphenidate group also showed an increased number of awakenings in comparison to the control group.

Fig. 1 shows the higher variability of night awakenings observed in the epilepsy + ADHD groups compared with controls; the most prominent was the group without methylphenidate.

The analysis of the SDSC (Table 4) scale showed that the, epilepsy + ADHD without methylphenidate had more sleep alterations: disorders of initiating and maintaining sleep, disorders of arousal, sleep-wake transition disorders, and sleep hyperhidrosis;

Table 3
Sleep organization based on actigraphy monitoring.

Variables#	Epilepsy + ADHD without methylphenidate (1) ($n = 21$)	ADHD with methylphenidate (2) ($n = 21$)	Epilepsy + ADHD with methylphenidate (3) ($n = 21$)	Control (4) ($n = 21$)	Significant differences	p
Total sleep time (minutes)	479.1 ± 59.0	465.6 ± 44.4	484.9 ± 66.2	455.4 ± 42.3	–	0.286*
Total time in bed (minutes)	525.3 ± 54.9	507.5 ± 48.9	536.0 ± 72.8	501.3 ± 41.6	–	0.168*
Sleep efficiency (%)	91.0 ± 4.2	91.8 ± 3.6	90.6 ± 4.3	90.8 ± 1.9	–	0.733*
Sleep latency (min)	11.1 ± 2.9	10.8 ± 4.8	10.0 ± 4.4	10.3 ± 2.3	–	0.804*
Night awakenings	2.6 (1.3–3.5)[c]	1.8 (0.6–2.5)[ab]	1.8 (0.9–2.7)[bc]	1.0 (0.5–1.5)[a]	1 > 2 and 4 3 > 4	0.001**

#Described by mean ± SD or median (percentile 25–75).
[a,b,c] Equal letters do not differ by Mann–Whitney test at 5% significance.
*One-way analysis of variance (ANOVA).
**Kruskal–Wallis test.

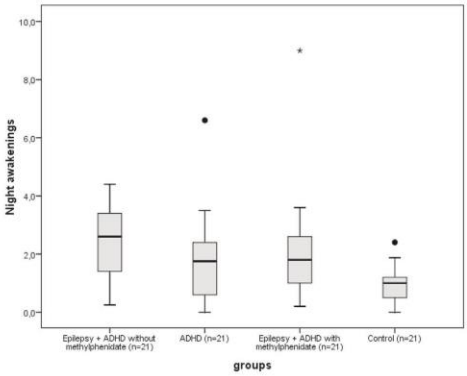

Fig. 1. Number of night awakenings per study group.

furthermore, there was a higher prevalence of sleep breathing disorders. The analysis also showed increased risk of sleep disorders in the ADHD group.

Table 5 summarizes the sleep analysis of the ADHD subtypes. The combined ADHD type showed a better sleep efficiency in the epilepsy + ADHD without methylphenidate group; a higher number of night awakenings of the inattentive type was observed in the same group. On the other hand, greater sleep latency was noted in the inattentive ADHD patients of the pure ADHD group.

4. Discussion

This study evaluated the sleep characteristics and disorders of children/adolescents with ADHD and epilepsy using two methods: a parent questionnaire and actigraphy monitoring. Both methods identified the epilepsy with ADHD without methylphenidate group as the one with most sleep alterations. Although the quality of sleep in patients with refractory epilepsy and ADHD is a widely studied subject, there are few studies that demonstrate these findings in patients with non-refractory epilepsy and ADHD as a comorbidity of epilepsy, which shows the originality of this study.

For this reason, two different methods of sleep evaluation were used to enrich and correlate the findings. The use of actigraphy offers the advantage of allowing the patient to home monitor, which is cost-effective and in present agreement with subjective reports of sleep [35]. Moreover, recent data explored the degree of concordance between polysomnography and actigraphy in school-aged children, and showed similar findings on sleep quantity measures [36].

In the present study, the SDSC indicated that the epilepsy and ADHD without methylphenidate group had more indicators for sleep disorders. Cohen et al. [37] reported similar findings and used the same questionnaire in an age-similar population with various neurological disorders, including epilepsy and ADHD.

Due to circumstances of the population evaluated in the present study, all patients were using short-acting methylphenidate. Recent data suggest that the effect of methylphenidate on sleep is complex, and its influence is more likely to cause a behavioral adjustment than a pharmacological regulation of sleep [38–42]. Thus, it may contribute to a better quality of life for children and their families.

Table 4
Sleep disorders identified through the Sleep Disturbance Scale for Children.

Variables[a]	Epilepsy + ADHD without methylphenidate (1) ($n = 20$) n (%)	ADHD with methylphenidate (2) ($n = 20$) n (%)	Epilepsy + ADHD with methylphenidate (3) ($n = 20$) n (%)	Control (4) ($n = 21$) n (%)	Significant differences	p^c
DIMS						
Normal	6 (30.0)	5 (25.0)	7 (35.0)	21 (100)[b]	Risk: 1 > 4	
Risk	12 (60.0)[b]	11 (55.0)	8 (40.0)	0 (0.0)		<0.001
SD	2 (10.0)	4 (20.0)	5 (25.0)	0 (0.0)		
SBD						
Normal	4 (20.0)	10 (50.0)	8 (40.0)	21 (100)[b]	SD: 1 > 4	
Risk	9 (45.0)	7 (35.0)	9 (45.0)	0 (0.0)		<0.001
SD	7 (35.0)[b]	3 (15.0)	3 (15.0)	0 (0.0)		
DA						
Normal	10 (50.0)	12 (60.0)	13 (65.0)	21 (100)[b]	Risk: 1 > 4	
Risk	9 (45.0)[b]	6 (30.0)	4 (20.0)	0 (0.0)		0.009
SD	1 (5.0)	2 (10.0)	3 (15.0)	0 (0.0)		
SWTD						
Normal	3 (15.0)	8 (40.0)	6 (30.0)	21 (100)[b]	Risk: 1 > 4	
Risk	9 (45.0)[b]	4 (20.0)	8 (40.0)	0 (0.0)		<0.001
SD	8 (40.0)	8 (40.0)	6 (30.0)	0 (0.0)		
DOES						
Normal	8 (40.0)	11 (55.0)	5 (25.0)	21 (100)[b]	Risk: 3 > 4	
Risk	9 (45.0)	8 (40.0)	11 (55.0)[b]	0 (0.0)		<0.001
SD	3 (15.0)	1 (5.0)	4 (20.0)	0 (0.0)		
SHY						
Normal	9 (45.0)	13 (65.0)	12 (60.0)	21 (100)[b]	Risk: 1 > 4	
Risk	9 (45.0)[b]	6 (30.0)	5 (25.0)	0 (0.0)		0.009
SD	2 (10.0)	1 (5.0)	3 (15.0)	0 (0.0)		
Total						
Normal	2 (10.0)	3 (15.0)	4 (20.0)	21 (100)[b]	Risk: 1 and 2 > 4	
Risk	14 (70.0)[b]	13 (65.0)[b]	10 (50.0)	0 (0.0)		<0.001
SD	4 (20.0)	4 (20.0)	6 (30.0)	0 (0.0)		

SD, sleep disorder; DIMS, disorders of initiating and maintaining sleep, SHY, sleep hyperhidrosis; SBD, sleep breathing disorders; DA, disorders of arousal; SWTD, sleep-wake transition disorders; DOES, disorders of excessive somnolence.

[a] Described by n (%).

[b] Statistically significant association for the adjusted residual test to 5% significance.

[c] Chi-squared test.

Table 5
Sleep organization based on actigraphy monitoring.

Variables	Epilepsy + ADHD without methylphenidate ($n = 21$)			ADHD with methylphenidate ($n = 21$)			Epilepsy + ADHD with methylphenidate ($n = 21$)		
	Inattentive	Combined	p	Inattentive	Combined	p	Inattentive	Combined	p
Total sleep time (minutes)	472.4 ± 59.4	500.5 ± 58.7	0.366[a]	456.7 ± 46.1	490.7 ± 35.6	0.126[a]	473.9 ± 62.9	522.9 ± 81.6	0.203[a]
Total time in bed (minutes)	524.3 ± 58.5	528.7 ± 47.2	0.880[a]	501.9 ± 55.1	520.9 ± 37.2	0.455[a]	524.4 ± 67.5	563.4 ± 94.3	0.351[a]
Sleep efficiency (%)	89.9 ± 3.9	94.4 ± 2.9	0.034[a]	91.1 ± 3.1	94.2 ± 3.8	0.065[a]	90.4 ± 4.2	93.3 ± 3.0	0.216[a]
Sleep latency (minutes)	11.6 ± 2.7	9.5 ± 3.2	0.174[a]	12.3 ± 4.7	6.8 ± 3.3	0.018[a]	10.8 ± 4.3	5.8 ± 1.9	0.040[a]
Night awakenings	2.7 (1.5–3.7)	1.0 (0.5–2.4)	0.025[b]	1.5 (0.6–2.6)	1.2 (0.2–2.5)	0.659[b]	1.9 (1.2–2.6)	1.1 (0.5–3.1)	0.494[b]

[a] Student's t-test.
[b] Mann–Whitney test.

Recent studies have evaluated sleep in ADHD patients and the influence of methylphenidate [38–42]. Some authors have found that methylphenidate can improve some sleep-related symptoms, such as decreased nighttime awakenings, sleepwalking and bed-wetting [39,40]. Konofal et al. point out that is necessary, at least in some children, to see ADHD as a "24-h" disorder, and increased nocturnal activity can lead to sleep disruption and then contribute to daytime symptomatology [39]. Likewise, Sangal et al. compared the effects of atomoxetine and methylphenidate on the sleep of children with ADHD [40]. Among the main findings, both medications decreased nighttime awakenings, but the greatest decrease was observed with methylphenidate.

Vigliano et al. compared sleep organization (using polysomnography), in children with ADHD before and after treatment with short-acting methylphenidate; more fragmented and less effective sleep before treatment were reported [41]. Becker et al. studied children with previous sleep complaints using long-acting methylphenidate; the majority improved after treatment [38]. Kim et al. evaluated the effect of OROS methylphenidate (CONCERTA®) on sleep quality, using both a sleep questionnaire and polysomnography; they also found a decreased number of awakenings [42].

Another relevant point to be considered is the perception of the "safe" use of methylphenidate in patients with epilepsy. A major concern in daily clinical practice is the decision to treat patients with epilepsy or those with epileptiform EEG abnormalities with psychostimulant drugs. Widely used guidelines are the Physician's Desk Reference and UP to Date, which they describe how methylphenidate causes a reduction in the threshold for seizures. These descriptions are based on case-report studies or animal studies that have been exposed to high doses of this drug [43]. Although there is a lack of controlled studies, the data that are now available show that when crises are controlled and this control is stable for a long period, methylphenidate has not been associated with recurrence of a crisis [44,45].

The influence of methylphenidate on seizure relapse was evaluated in two recent studies. In agreement with the present results, besides the improvement of ADHD symptoms, no increase in seizure frequency or severity was observed [44,46].

Limitations of the present study were: the high variance of age among the subjects, and lack of comparison of anticonvulsants and methylphenidate dosages.

In conclusion, these findings show that primary ADHD or ADHD as a comorbidity of epilepsy impairs sleep organization in children, and the use of short-acting methylphenidate seems to improve it. Both objective (actigraphic) and subjective (SDSC) measures showed significant sleep alterations between primary ADHD and ADHD as a comorbidity of epilepsy, the most prominent being in the epilepsy + ADHD without methylphenidate group.

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Transparency document

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2016.08.013.

Conflict of interest

The authors have no conflict of interest or disclosures to declare.

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CAPÍTULO IV

4.1 CONCLUSÕES

Existem diferenças significativas entre o sono de crianças/adolescentes com TDAH primário e TDAH como comorbidade da epilepsia tanto em medidas objetivas (actigrafia) quanto subjetivas (escala de sono).

Nos achados da actigrafia foi observado aumento significativo no número de despertares noturnos principalmente no grupo de pacientes com epilepsia/TDAH sem uso de metilfenidato, tanto em relação aos controles quanto ao grupo TDAH primário. Os pacientes do grupo epilepsia/TDAH com uso de metilfenidato também apresentaram aumento do número de despertares em relação ao grupo controle

As demais variáveis aferidas pelo uso do actígrafo (tempo total do sono, período total do sono, eficiência do sono e latência do sono) não evidenciaram diferenças significativas entre os grupos em estudo.

Na análise da escala de sono, da mesma forma que na actigrafia, o grupo que apresentou maior número de alterações foi o epilepsia/TDAH sem uso de metilfenidato. Este grupo apresentou risco aumentado para distúrbios de início e manutenção do sono (DIMS), distúrbios do despertar (DD), distúrbios da transição sono-vigília (DTSV) e hiperidrose do sono (HS); além disso, foi observada maior prevalência de distúrbios respiratórios do sono (DRS). Na análise total (avaliação do risco médio total de desenvolver doenças por grupo), o grupo TDAH também apresentou risco aumentado para distúrbios do sono.

A avaliação da influência do uso de metilfenidato na qualidade do sono em pacientes com epilepsia e TDAH evidenciou que o grupo que não fez uso de metilfenidato de curta ação (grupo epilepsia/TDAH sem metilfenidato) foi o que apresentou maiores alterações tanto na actigrafia como na escala de sono.

ANEXO

ANEXO - APROVAÇÃO CEP

PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL - PUC/RS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação da qualidade do sono em pacientes com epilepsia e Transtorno do Déficit de Atenção e Hiperatividade (TDAH)

Pesquisador: Magda Lahorgue Nunes

Área Temática:

Versão: 1

CAAE: 35171914.2.0000.5336

Instituição Proponente: UNIAO BRASILEIRA DE EDUCACAO E ASSISTENCIA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 800.905

Data da Relatoria: 12/09/2014

Apresentação do Projeto:

O projeto visa avaliar a qualidade e arquitetura do sono em pacientes de 7 a 18 anos com epilepsia controlada há 3 meses em monoterapia e TDAH em tratamento com metilfenidato, pacientes com epilepsia controlada há 3 meses com monoterapia e TDAH sem tratamento, pacientes com TDAH e pacientes controle, sendo 4 grupos com 21 pacientes para significância de 5% no estudo estatístico. O estudo do sono será feito com actígrafo durante 5 dias após uma avaliação do distúrbio de sono com entrevistas e questionário de sono. O actígrafo foi obtido através de PROEX/CAPES 2013.

Objetivo da Pesquisa:

Avaliação de sono em epilepsia e TDAH com técnica rescente com actígrafo. Registro ambulatorial.

Avaliação dos Riscos e Benefícios:

Sem riscos. Questionários e registro com actígrafo. Benefício de utilização de nova técnica de registro do sono ambulatorial.

Comentários e Considerações sobre a Pesquisa:

Utilização de técnica nova de registro ambulatorial de qualidade e arquitetura do sono com actígrafo.

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Bairro: Partenon **CEP:** 90.619-900
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PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL - PUC/RS

Continuação do Parecer: 800.905

Considerações sobre os Termos de apresentação obrigatória:

Adequados.Apresentados termos de consentimento e assentimento.

Recomendações:

Sem pendências.

Conclusões ou Pendências e Lista de Inadequações:

Sem pendências.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

PORTO ALEGRE, 23 de Setembro de 2014

Assinado por:
Rodolfo Herberto Schneider
(Coordenador)

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