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Maria*

- Antecedentes de muitas visitas à emergência
- Sofreu breves perdas de consciência
- Chegou com níveis máximos terapêuticos de fenitoína
- Polimedicada

*Não é uma paciente real

VIMPAT IV: ALTERNATIVA EFICAZ QUANDO A ADMINISTRAÇÃO ORAL NÃO É VIÁVEL.[1]

VIMPAT solução para infusão 10 mg/mL.

- VIMPAT é indicado como terapia adjuvante no tratamento de crises parciais com ou sem generalização secundária em pacientes a partir de 16 anos de idade com epilepsia.[1]
- A conversão da administração por via oral para a intravenosa ou vice-versa, pode ser feita diretamente sem ajuste da dose.[1]
- Baixo potencial de interações medicamentosas farmacocinéticas com outros FAEs concomitantes.[1,2]
- Se caracteriza pelo seu perfil farmacocinético favorável, segurança e tolerabilidade.[1,3]

VIMPAT™ lacosamida

CONTRAINDICAÇÃO: em casos de hipersensibilidade ao princípio ativo (lacosamida) ou a qualquer um dos excipientes.
INTERAÇÃO MEDICAMENTOSA: medicamentos conhecidos por prolongar o intervalo PR e antiarrítmicos classe I.

Referências Bibliográficas: 1. Vimpat solução para infusão IV 10mg/mL. Informação para prescrição. Reg. MS –1.2361.0081. **2.** Wheless JW, Venkataraman V. New formulations of drugs in epilepsy. Expert Opin Pharmacother.1999;1:49-60. **3.** Chung S, et al. Examining the clinical utility of lacosamide: pooled analyses of three phase II/III clinical trials. CNS Drugs. 2010;24(12):1041-54.

Vimpat™ (lacosamida) solução para infusão 10mg/mL em embalagem com 1 frasco-ampola de 20mL. **Indicações:** terapia adjuvante no tratamento de crises parciais com ou sem generalização secundária em pacientes a partir de 16 anos de idade com epilepsia. **Contraindicações:** em casos de hipersensibilidade ao princípio ativo (lacosamida) ou a qualquer um dos excipientes. **Cuidados e Advertências:** Advertências (vide bula completa do produto): **Vimpat** pode causar tonturas, que podem aumentar o risco de acidente ou queda. Um pequeno número de pessoas que iniciaram tratamento com antiepilépticos, como a lacosamida, apresentou pensamentos de autoagressão ou suicídio. Não é recomendável tomar **Vimpat** com álcool, pois **Vimpat** pode provocar tonturas ou sensação de cansaço. **Vimpat** é um medicamento. Durante seu uso, não dirija veículos ou opere máquinas, pois sua agilidade e atenção podem estar prejudicadas. Nos estudos clínicos foram observados prolongamentos no intervalo PR com o uso de lacosamida. Bloqueio AV de segundo grau ou maior foi reportado na experiência pós-comercialização. Gravidez: categoria C de risco de gravidez. Interações medicamentosas (vide bula completa do produto): A lacosamida deve ser usada com cautela em pacientes tratados com medicamentos conhecidos por prolongar o intervalo PR e em pacientes tratados com medicamentos antiarrítmicos classe I. Dados in vitro sugerem que a lacosamida possui potencial para inibir CYP2C19 em concentrações terapêuticas. A análise farmacocinética populacional estimou que o tratamento concomitante com outros medicamentos antiepilépticos indutores enzimáticos (carbamazepina, fenitoína, fenobarbital, em várias doses) reduz a exposição sistêmica geral da lacosamida em 25%. Reações adversas (vide bula completa do produto): Muito comuns: tontura, dor de cabeça, náusea e diplopia. Comuns: distúrbio cognitivo, nistagmo, distúrbio de equilíbrio, coordenação anormal, falha de memória, tremor, sonolência, disartria, distúrbio de atenção, hipoestesia, parestesia, visão embaçada, vertigem, zumbido, vômitos, constipação, flatulência, dispepsia, boca seca, diarreia, prurido, espasmos musculares, distúrbio ao andar, astenia, fadiga, irritabilidade, sensação de embriaguez, quedas, laceração da pele, contusão. **Posologia:** A dose inicial recomendada é de 50 mg duas vezes por dia, a qual deverá ser aumentada para uma dose terapêutica inicial de 100 mg duas vezes por dia após uma semana. O tratamento com lacosamida também pode ser iniciado com uma dose de carga única de 200 mg, seguida por uma dose de regime de manutenção, após aproximadamente 12 horas, de 100 mg duas vezes ao dia (200 mg/dia). A dose de carga deve ser administrada sob supervisão médica considerando sua farmacocinética e o potencial para o aumento de incidência de reações adversas relacionadas ao SNC. A administração da dose de carga não foi estudada em condições agudas em estados epilépticos. Dependendo da resposta clínica e tolerabilidade, a dose de manutenção pode ser aumentada 50 mg, duas vezes por dia, a cada semana, até uma dose diária máxima de 400 mg (200 mg duas vezes por dia. **USO ADULTO E PEDIÁTRICO ACIMA DE 16 ANOS DE IDADE. USO INTRAVENOSO. USO RESTRITO A HOSPITAIS. VENDA SOB PRESCRIÇÃO MÉDICA – SÓ PODE SER VENDIDO COM RETENÇÃO DA RECEITA. SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO.** Para maiores informações, consulte a bula completa do produto. (0302040012R4 Rev. Fevereiro 2014). www.ucb.com **Reg. MS – 1.2361.0081**

JECN Journal of Epilepsy and Clinical Neurophysiology

Órgão Oficial da Liga Brasileira de Epilepsia

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JECN Journal of Epilepsy and Clinical Neurophysiology

Instructions for authors / Instruções aos autores / Instrucciones para los autores

Most recent revision: March 2015

The Journal of Epilepsy and Clinical Neurophysiology (JECN) is the Official Body of the Brazilian Epilepsy League, whose purpose is to publish original scientific-technological articles about epilepsy and clinical neurophysiology, resulting from ethically developed and approved clinical and experimental research. Volumes are published annually, with quarterly editions, in March, June, September and December of each year. The articles submitted must be original and concise, written in English, Portuguese or Spanish. The text should be prepared in accordance with the technical standards, and sent via the publications management system. In order to be approved, the articles will be submitted for evaluation by a panel of reviewers (peer review), who will receive the text anonymously and decide on its publication, suggest changes, request clarification from the authors, and provide recommendations to the Editor-in-Chief. The concepts and statements contained in the work are the sole responsibility of the authors. The Journal Epilepsy and Clinical Neurophysiology follows, in full, the international trend of the Vancouver style, which is available at www.icmje.org.br. We thank the authors, in advance, for their collaboration in following the instructions.

FORMATTING OF ARTICLES

LIMITS FOR EACH TYPE OF PUBLICATION (Extension): The following criteria must be observed for each type of publication. The electronic word count must include: the title page and text.

Type of Article	Abstract	Number of words	References	Figures	Tables
Original	Structured with up to 250 words	6.000 not including the abstract, references, tables and figures	45	10	6
Update / Review Case Report	It is not structured with up to 250 words	6.000 not including the abstract, references, tables and figures	60	3	2
Editorial	0	500	5	0	0

MANUSCRIPT PREPARATION: The Journal of Epilepsy and Clinical Neurophysiology receives the following types of manuscript for publication: Original Articles, Update and Reviews Articles, Case Report, Editorial. The manuscripts should be submitted in accordance with PC standard, in Word files, double spaced, with wide margins, and the author shall include a signed letter of authorization for publication, declaring that it is an original work, and that it has not been, or is not being submitted for publication in any other journal. Ensure that the manuscript is fully in accordance with the instructions.

CLINICAL TRIALS: The Journal of Epilepsy and Clinical Neurophysiology supports the policies for the recording of clinical trials of the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE), recognizing the importance of these initiatives for the recording and international disclosure of information on clinical trials, in open access. Accordingly, only clinical research articles that have received an identification number in one of the Clinical Trial Records validated by the WHO and ICMJE criteria will be accepted for publication. The addresses for these records are available on the ICMJE website (www.icmje.org). The identification number should be declared in the text.

CONFLICTS OF INTEREST: According to the requirements of the International Committee of Medical Journal Editors (ICMJE), the Vancouver group, and Resolution no. 1595/2000 of the Federal Council of Medicine Resolution, the authors have a responsibility to recognize and declare any conflicts of interest, financial or otherwise (business, personal, political, etc.) involved in the development of work submitted for publication. The authors must declare, and may acknowledge, in the manuscript, any financial support received for the work, as well as others parties involved in its development.

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COVER PAGE: The cover page must include:

a) type of article (original article, review or update)

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c) full name of each author (without abbreviations); and the institution to which each one belongs

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ABSTRACT: The Abstract must be structured in the case of original articles, and must clearly present the study objectives, with historical data, methods, results, and the main conclusions. It must be written Portuguese, English and Spanish, and should not exceed 200 words.

DESCRIPTORS: Must contain at least three key words in Portuguese based on the Health Sciences Descriptors (DeCS) -http://decs.bireme.br. In English, submit keywords based on the Medical Subject Headings (MeSH) - http://www.nlm.nih.gov/mesh/meshhome.html, at least three and at most six citations.

INTRODUCTION: Present the subject and purpose of the study, and provide citations, without giving an external review of the subject.

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ACKNOWLEDGEMENT: Addressed to persons who have collaborated intellectually but whose contribution does not constitute co-authorship, or those who have provided material support.

REFERENCES: Quote up to about 20 references, restricted to the bibliography essential to the content of the article. Number references consecutively in the order in which they are mentioned in the text, using superscript Arabic numerals, in the following format: (Reduction of functions of the terminal plate.[1]) Give the names of the first three authors, followed by et al.

Journal titles should abbreviated, according to the Index Medicus.

a) Articles: Author(s). Title of the article. Title of the Journal. year; volume: first-last age E.g. Campbell CJ. The healing of cartilage defects. Clin Orthop Res Report. 1969;(64):45-63.

b) Books: Author(s) or editor(s). Title of the book. Edition, if not the first. Translator(s), if applicable. Place of publication: publisher, year. E.g. Diener HC, Wilkinson M, editors. Drug-induced headache. 2nd ed. New York: Spriger-Verlag; 1996.

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e) Personal communications should only be mentioned in the text in parentheses.

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A Revista Journal of Epilepsy and Clinical Neurophysiology (JECN) é o Órgão Oficial da Liga Brasileira de Epilepsia, cujo propósito é publicar artigos científico-tecnológicos originais sobre epilepsia e neurofisiologia clínica, resultante de pesquisas clínicas e experimentais, eticamente desenvolvidas e aprovadas. Os volumes são publicados anualmente, com edições trimestrais em março, junho, setembro e dezembro de cada ano. Os artigos submetidos devem ser inéditos e concisos, redigidos em inglês, português ou espanhol. O texto deverá ser preparado de acordo com as normas técnicas e enviados pelo sistema de gerenciamento de publicações. Os artigos para serem aprovados são submetidos à avaliação de uma comissão de revisores (peer review) que recebem o texto de forma anônima e decidem por sua publicação, sugerem modificações, requisitam esclarecimentos aos autores e efetuam recomendações ao Editor Chefe. Os conceitos e declarações contidos nos trabalhos são de total responsabilidade dos autores. A Journal of Epilepsy and Clinical Neurophysiology segue na íntegra a tendência internacional do estilo Vancouver, disponível (www.icmje.org.br). Desde já agradecemos a colaboração dos autores no atendimento às instruções citadas.

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Original	Estruturado com até 250 palavras	6.000 Excluindo o resumo, referências, tabelas e figuras	45	10	6
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PREPARAÇÃO DE MANUSCRITO: A Journal of Epilepsy and Clinical Neurophysiology recebe para publicação os seguintes tipos de manuscritos: Artigo Original, Artigo de Atualização e Revisão, Relato de Caso. Os manuscritos enviados deverão estar em padrão PC com arquivos em *Word*, espaço duplo, com margem larga, devendo o autor inserir carta assinada, autorizando sua publicação, declarando que o mesmo é inédito e que não foi, ou está sendo submetido à publicação em outro periódico. Certifique-se de que o manuscrito se conforma inteiramente às instruções.

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a) o tipo do artigo (artigo original, de revisão ou atualização);

b) o título completo em português, inglês e espanhol com até 120 caracteres deve ser conciso, porém informativo;

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e) nome, endereço, telefone e e-mail do autor responsável para correspondência.

RESUMO: O Resumo deve ser estruturado em caso de artigo original e deve apresentar os objetivos do estudo com clareza, dados históricos, métodos, resultados e as principais conclusões em português, inglês e espanhol, não devendo ultrapassar 200 palavras.

DESCRITORES: Deve conter no mínimo três palavras chaves baseadas nos Descritores de Ciências da Saúde (DeCS) -http://decs.bireme.br. No inglês, apresentar keywords baseados noMedical Subject Headings (MeSH) - http://www.nlm.nih.gov/mesh/meshhome.html, no mínimo três e no máximo seis citações.

INTRODUÇÃO: Deve apresentar o assunto e objetivo do estudo, oferecer citações sem fazer uma revisão externa da matéria.

MATERIAL E MÉTODO: Deve descrever o experimento (quantidade e qualidade) e os procedimentos em detalhes suficientes que permitam a outros pesquisadores reproduzirem os resultados ou darem continuidade ao estudo. Ao relatar experimentos sobre temas humanos e animais, indicar se os procedimentos seguiram as normas do Comitê Ético sobre Experiências Humanas da Instituição, na qual a pesquisa foi realizada ou de acordo com a declaração de Helsinki de 1995 e Animal Experimentation Ethics, respectivamente. Identificar precisamente todas as drogas e substâncias químicas usadas, incluindo os nomes genéricos, dosagens e formas de administração. Não usar nomes dos pacientes, iniciais, ou registros de hospitais. Oferecer referências para o estabelecimento de procedimentos estatísticos.

RESULTADOS: Apresentar os resultados em sequência lógica do texto, usando tabelas e ilustrações. Não repetir no texto todos os dados constantes das tabelas e ou ilustrações. No texto, enfatizar ou resumir somente as descobertas importantes.

DISCUSSÃO: Enfatizar novos e importantes aspectos do estudo. Os métodos publicados anteriormente devem ser comparados com o atual para que os resultados não sejam repetidos.

CONCLUSÃO: Deve ser clara e concisa e estabelecer uma ligação entre a conclusão e os objetivos do estudo. Evitar conclusões não baseadas em dados.

AGRADECIMENTOS: Dirigidos a pessoas que tenham colaborado intelectualmente, mas cuja contribuição não justifica coautoria, ou para aquelas que tenham provido apoio material.

REFERÊNCIAS: Citar até cerca de 20 referências, restritas á bibliografia essencial ao conteúdo do artigo. Numerar as referências de forma consecutiva de acordo com a ordem em que forem mencionadas pela primeira vez no texto, utilizando-se números arábicos sobrescritos, no seguinte formato: (Redução das funções da placa terminal.[1]) Incluir os três primeiros autores seguidos de et al.

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Ex.: Campbell CJ. The healing of cartilage deffects. Clin Orthop Relat Res. 1969;(64):45-63.

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JECN Journal of Epilepsy and Clinical Neurophysiology

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Original Article/Artigo Original/Artículo Original

EPILEPSY AND HYPOTHYROIDISM IN CHILDREN WITH DOWN SYNDROME

EPILEPSIA E HIPOTIREOIDISMO EM CRIANÇAS COM SÍNDROME DE DOWN

EPILEPSIA E HIPOTIROIDISMO EN NIÑOS CON SÍNDROME DE DOWN

Ana Batschauer[1], Paulo Breno Noronha Liberalesso[1,2], Alexandre Menna Barreto[3], Jair Mendes Marques[2], Bianca Simone Zeigelboim[2], Eliana Garzon[4]

ABSTRACT

Objective: This paper presents a review of epilepsy and thyroid dysfunction in children with Down syndrome and analyzes the possible association between these comorbidities. Methods: The medical records of all patients with Down syndrome treated at the Pediatric Neurology Department of Pequeno Príncipe Children's Hospital e from January 2008 to January 2014 (72 patients) were analyzed and divided into two groups: one consisting of patients with Down syndrome and epilepsy (GROUP I), and the other of patients with Down syndrome and without epilepsy (GROUP II). The two groups were then compared with respect to the prevalence of thyroid dysfunction. The association of the mother's age at the child's birth and the presence of epilepsy and/or thyroid dysfunction were also tested. Results: The data showed that among children with Down syndrome there is no significant association (p=0.09) between the presence or absence of epilepsy and the presence or absence of hypothyroidism. In addition, no significant association was found between the mother's age at the child's birth (<35 or ≥35 years) and an increased risk of epilepsy (p=0.37) nor an increased risk of hypothyroidism (p=0.42). Conclusions: Our study found no significant association between the two comorbidities, epilepsy and thyroid dysfunctions, in people with DS, or significant relationship of each one individually with the mother's age at the child's birth in this population.

Keywords: Down syndrome; Thyroid gland; Epilepsy.

RESUMO

Objetivo: Este artigo apresenta uma revisão sobre epilepsia e disfunção tireoidiana em crianças com síndrome de Down e analisa uma possível associação entre estas duas comorbidades. Métodos: Foram analisados todos os prontuários médicos de pacientes com síndrome de Down tratados no Departamento de Neurologia Pediátrica do Hospital Infantil Pequeno Príncipe entre janeiro de 2008 e janeiro de 2014 (72 pacientes), e divididos em dois grupos: um de pacientes com síndrome de Down e epilepsia (GRUPO I) e outro de pacientes com síndrome de Down e sem epilepsia (GRUPO II). Os dois grupos foram comparados quanto à disfunção tireoidiana. A associação entre a idade materna ao nascimento da criança e a presença de epilepsia e/ou disfunção tireoidiana também foi testada. Resultados: Os dados mostram que nas crianças não há associação significativa (p=0,09) entre a presença ou ausência de epilepsia e a presença ou ausência de hipotireoidismo. Além disso, não há associação significativa entre a idade da mãe ao nascimento da criança (< 35 ou ≥ 35 anos) e aumento do risco de epilepsia (0=0,37) nem aumento do risco de hipotireoidismo (p=0,42). Conclusões: Nosso estudo não encontrou associação significativa entre as duas comorbidades, epilepsia e disfunção tireoidiana, em pessoas com síndrome de Down nem relação significativa de cada um individualmente com a idade da mãe ao nascimento da criança nesta população.

Descritores: *Síndrome de Down; Glândula tireoide; Epilepsia.*

RESUMEN

Objetivo: Este artículo presenta una revisión sobre epilepsia y disfunción tiroidea en niños con síndrome de Down y analiza una posible asociación entre estas dos comorbidades. Métodos: Fueron analizados todos los prontuarios médicos de pacientes con síndrome de Down tratados

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en el Departamento de Neurología Pediátrica del Hospital Infantil Pequeno Príncipe entre enero de 2008 y enero de 2014 (72 pacientes), y divididos en dos grupos: uno con pacientes con síndrome de Down y epilepsia (GRUPO I) y otro con pacientes con síndrome de Down y sin epilepsia (GRUPO II). Los dos grupos fueron comparados cuanto a la disfunción tiroidea. La asociación entre la edad materna en el nacimiento del niño y la presencia de epilepsia y/o disfunción tiroidea también fue probada. Resultados: Los datos muestran que en los niños no hay asociación significativa (p = 0,09) entre la presencia o ausencia de epilepsia y la presencia o ausencia de hipotiroidismo. Además, no hay asociación significativa entre la edad de la madre en el nacimiento del niño (< 35 ó ≥ 35 años) y aumento del riesgo de epilepsia (0=0,37) ni aumento del riesgo de hipotiroidismo (p = 0,42). Conclusiones: Nuestro estudio no encontró asociación significativa entre las dos comorbidades, epilepsia y disfunción tiroidea, en personas con síndrome de Down ni relación significativa de cada uno individualmente con la edad de la madre en el nacimiento del niño en esta población.

Descriptores: *Síndrome de Down; Glándula tiroides; Epilepsia.*

INTRODUCTION

Down's syndrome (DS) was described originally in 1866 by British physician John Langdon Down. It is considered the most frequent and well known chromosomal abnormality, with an incidence varying according to maternal age from 1:2000 live births at the beginning of the fertile life to 1:40 in pregnant women over 40 years.[1,2] Most cases are caused by a mechanism of non-disjunction leading to trisomy 21, although cases of on unbalanced translocation involving chromosome 21 and some other chromosome, and mosaicism may occur.[2,3]

A major cause of mental retardation of prenatal origin, DS often has several associated comorbidities, including: congenital heart defects, such as ventricular septal defect, atrioventricular canal defect and patent ductus arteriosus; problems with the gastrointestinal tract, such as duodenal atresia and aganglionar bowel disease; hearing problems; vision problems, such as cataracts, strabismus and refractive optical defects; early degeneration of the musculoskeletal system, with atlanto-axial subluxation and collapse of vertebral bodies; endocrine diseases, such as diabetes and thyroid dysfunction (hypothyroidism or hyperthyroidism); leukemias and solid tumors; immunological changes; neurological problems, such as epilepsy and early-onset dementia of the Alzheimer type; obesity and premature aging. These conditions may pose hazards to health of these children and shorter survival.[2,4-6]

Epilepsy and thyroid dysfunction stand out among the comorbidities previously mentioned, because of their high prevalence and serious health repercussions in the affected individuals. Although seizures are not present among the clinical findings in the original description of the syndrome, it is currently known that they are significantly more frequent in children with DS than in the general population, and less frequent than in patients with mental disabilities related to other etiologies.[1,2,5]

Given the findings of the last decade in relation to the significant percentage of children with DS and epilepsy (approximately 1 in 10), it is clear that physicians should suspect the possibility of epilepsy and intervene as early as possible when seizures are suspected, to maximize the patient´s development and improve quality of life as much as possible.[5]

Involuntarily, the association between DS and thyroid dysfunction was first proposed in 1866 by Seguin, who described the condition as "furfuraceus" cretinism, in an attempt to differentiate it from that of "stable" cretins. At the turn of the twentieth century, Bournville (1903) described the pathological association between DS and thyroid dysfunction, which was soon followed by clinical and histopathologic confirmation. However, the first case report of a person with DS and clinical hyperthyroidism was realized by Gilchrist (1946), and of a person with DS and hypothyroidism, by Maranon (1951). At the turn of the third millennium, thyroid dysfunction in people with DS continues to be the focus of ongoing interest and research.[3]

A review of literature on the subject shows that 3 to 54% of people with DS have biochemical evidence of hypothyroidism, with increased lifetime prevalence. Both hypothyroidism and hyperthyroidism are more common in people with DS than in the general population.[3,7,8]

The recognition of thyroid dysfunction may be rather difficult in people with DS, taking into consideration that clinical symptoms and signs of both conditions overlap in several respects. Either hypothyroidism or DS may present, for example, hypotonia, lethargy, dullness, mental retardation, growth failure, prolonged neonatal jaundice, delayed closure fontanellae, macroglossia, obesity etc.[3,7,9] The delay in the diagnosis of hypothyroidism leads to an aggravation of the already fragil health situation of this population.[9]

There are several reports of people with DS and thyroid dysfunction in association with other clinical conditions. Regarding thyroid dysfunction and epilepsy, yet little is known about their coexistence and relation with each other in this population.

This paper aims to explore this issue. It presents a review of epilepsy and thyroid dysfunction in children with DS and analyzes the possible association between these comorbidities in this population, also evaluating the influence of the mother's age at the child's birth regarding development with these clinical conditions.

METHODS

The study is observational and cross-sectional. Medical records of all patients with DS treated at the Pediatric Neurology Department of Pequeno Príncipe Children's Hospital from January 2008 to January 2014 were analyzed, totaling 72 patients. The only criteria for inclusion in the study were the presence of DS and the fact of being accompanied at the health service and within the period of time aforementioned. The patients participating in this study had no financial outlay.

The data collected included the following variables: sex, age, presence or absence of epilepsy, age at first seizure, epilepsy classification, the first electroencephalogram (EEG), cranial tomography (CT), magnetic resonance imaging (MRI), thyroid function (normal, hypothyroidism or hyperthyroidism) and the mother's age at the child's birth. All EEG were performed with a minimum duration of 30 minutes, and with electrodes positioned according to the International 10-20 System (an internationally recognized method to describe the location of scalp electrodes), in digital EEG monitoring equipments with 21 channels (Nihon Koden®, Neurotec® and Neurovirtual

Brain Wave II®). For analysis of thyroid hormones, normal reference values were considered: free thyroxine fraction (free-T4) – 0.8 a 1.75 ng/dl and thyroid-stimulating hormone (TSH) – 0.6 a 6.30 UI/ml.

After data collection, patients were divided into two groups, one consisting of patients with DS and epilepsy (*GROUP I*), and the other of patients with DS and without epilepsy (*GROUP II*), and then each group was compared to the other with respect to the prevalence of thyroid dysfunction (hypothyroidism or hyperthyroidism). The influence of the mother's age at the child's birth with regard to the presence of epilepsy and/or thyroid dysfunction was also tested. Data analysis used the methodology of descriptive statistics and Chi-square test at a significance level of 0.05. The research protocol was approved by the Ethics Committee on Research Involving Human Subjects (registration number CEP 725.489/2014) at Pequeno Príncipe Children's Hospital.

RESULTS

Seventy-two patients with DS were included in the study and divided into two groups for analysis and comparison: *GROUP I* - patients with DS and epilepsy and *GROUP II* – patients with DS and without epilepsy.

GROUP I: 34 patients, 18 (52.94%) male and 16 (47.06%) female, aged between 20-88 months (mean 53.85 ± 21.59 months). The age at first seizure ranged from 3-53 months (mean 29.35 ± 20.60 months). The types of epilepsy were classified as West syndrome (5/14.70%), focal epilepsy (15/44.12%), multifocal epilepsy (4/11.76%) and generalized epilepsy (10/29.41%). The detailed classification of epilepsies and results of EEGs records are in Table 1. All patients performed CT examination, 21 (61.76%) normal, 10 (29.41%) brain atrophy, 1 (2.94%) left parietal gliosis, 1 (2.94%) left frontocentral gliosis and 1 (2.94%) left temporal gliosis. Eighteen patients were submitted to brain MRI, 9 (50%) normal, 4 (22.22%) cerebral atrophy, 2 (11.11%) cerebral atrophy and periventricular leukomalacia, 1 (5.55%) left parietal gliosis, 1 (5.55%) frontocentral and parietal gliosis and 1 (5.55%) left centrotemporal gliosis. Regarding the evaluation of thyroid function, 23 (67.65%) normal and 11 (32.35%) hypothyroidism. Mother's age at the child's birth ranged from 24-42 years (mean 33.94 ± 4.96 years).

GROUP II: 38 patients, 19 (50%) male and 19 (50%) female, aged between 18-95 months (mean 53.87 ± 20.53 months). Regarding the evaluation of thyroid function, 32 (84.21%) normal and 6 (15.79%) hypothyroidism. Mother's age at the child's birth ranged from 26-42 years (mean 34.29 ± 4.80 years).

GROUP I and GROUP II: with the use of Chi-square test at a significance level of 0.05, it was found that in children with DS there is no significant association (p=0.09) between the presence or absence of epilepsy and the presence or absence of hypothyroidism (Table 2), and there is also no significant association (p=0.37) between the mother's age the child's birth (<35 or ≥ 35 years) and the increased risk of epilepsy (p=0.37) (Table 3) and between the mother's age at the child's birth (<35 or ≥ 35 years) and the increased risk of hypothyroidism (p=0.42). (Table 4)

Table 1. Classification of epilepsies and EEGs records.

Patients	Classification of Epilepsies	EEGs records
1	Focal	BA-DD. SW - right frontocentral
2	West syndrome	BA-MD - hypsarrhythmia
3	West syndrome	BA-MD - hypsarrhythmia
4	Focal	BA-DD. SW - left frontocentral
5	Focal	BA-DD. SW - rigth frontal
6	Generalized	BA-DD. S, SW, PSW - generalized discharges
7	West syndrome	BA-MD - hypsarrhythmia
8	Focal	BA-DD. SW - right temporal
9	Generalized	BA-MD. S, SW, PSW - generalized discharges
10	Generalized	BA-MD. PSW - generalized discharges
11	Multifocal	BA-MD. SW - multifocal
12	Focal	BA-DD. SW - right parietal and occipital
13	Multifocal	BA-MD. SW - multifocal
14	Generalized	BA-MD. PSW - generalized discharges
15	Focal	BA-DD. SW - right frontal and parietal
16	Generalized	BA-DD. S, SW - generalized discharges
17	West syndrome	BA-MD - hypsarrhythmia
18	West syndrome	BA-MD - hypsarrhythmia
19	Focal	BA-MD. SW - right parietal and occipital
20	Multifocal	BA-MD. SW - multifocal
21	Generalized	BA-MD. S, SW, PSW - generalized discharges
22	Focal	BA-DD. SW - left central and parietal
23	Generalized	BA-MD. S - generalized discharges
24	Focal	BA-DD. SW - left parietal and occipital
25	Focal	BA-DD. SW- left central and parietal
26	Multifocal	BA-MD. SW - multifocal
27	Focal	BA-DD. SW - right central and parietal
28	Generalized	BA-MD. S - generalized discharges
29	Focal	BA-DD. SW - left frontal and central
30	Generalized	BA-DD. S - generalized discharges
31	Focal	BA-DD. SW - left parietal and occipital
32	Focal	BA-MD. SW - right parietal and occipital
33	Focal	BA-MD. SW - left temporal and parietal
34	Generalized	BA-DD. S - generalized discharges

Background activity - BA. Sharp wave discharges - SW. Discreetly disorganized - DD. Moderate disorganized - MD. Spike - S. Spike-wave - SW. Polispike-wave - PSW.

Table 2. Relationship between hypothyroidism and epilepsy.

	Hypothyroidism		Total
	Yes	No	
With epilepsy	11	23	34
Without epilepsy	6	32	38
Total	17	55	72

Significance level (p=0.09).

Table 3. Relationship between the mother's age at the child's birth and risk of epilepsy.

	Mother's age		Total
	under 35 years	35 years and over	
With epilepsy	17	17	34
Without epilepsy	15	23	38
Total	32	40	72

Significance level (p=0.37).

Table 4. Relationship between the mother's age at the child's birth and risk of hypothyroidism.

	Mother's age		Total
	Under 35 years	35 years and over	
Hypothyroidism	9	8	17
Normal	23	32	55
Total	32	40	72

Significance level (p=0.42).

DISCUSSION

Patients with DS often have comorbidities, among which stand out, because of their prevalence and serious repercussions on health situation, epilepsy and thyroid dysfunction. It is known that epilepsy is significantly more frequent in children with DS than in the general population and less frequent than in patients with mental disabilities related to other etiologies.[1,2,5,10]

The age of onset of seizures in people with DS is variable, with bimodal distribution with a first peak incidence in the first two decades of life, especially before one year of age, and a second peak starting from the third decade of life, especially in the fifth and sixth decades of life.[2,5,10] The prevalence of epilepsy increases with age, reaching 46% in those over 50 years.[5]

In our research, the age of onset of seizures ranged from 3 to 53 months (mean 29.35 months ± 20.60 months).

Boys tend to have earlier onset of seizures. This may reflect the male predominance in the group of infantile spasms, which usually occur in the first year of life[5]. The late onset of seizures is associated with increased susceptibility for the development of dementia of the Alzheimer type.[5,11]

Two aspects are relevant to explain the higher incidence of epilepsy in patients with DS: presence of other diseases or pathological conditions related to increased risk of seizures; structural and functional changes in the brain resulting from the syndrome itself. [2,5,10]

In relation to diseases or pathological conditions related to increased risk of seizures, a study demonstrated that 61.7% had definite or presumed etiology, including heart disease (hypoxia crises and arterial occlusion by thrombosis), perinatal complications at birth (bleeding and choking) and infections (febrile seizures, infections of the central nervous system and brain abscess).[5]

With respect to the structural and functional changes that may be present in the brain of patients with DS and influence the presence of seizures, we mention the lower number of GABAergic neurons in the cerebral cortex, abnormalities in calcium ion channels, changes in neurotransmitters (for example, the serotonin, an inhibitory neurotransmitter in various regions of the brain, which is present at lower levels in these people), lower neuronal density in the hippocampal, dendritic malformation, degeneration of pyramidal and extrapyramidal neurons, abnormal lamination of the cerebral cortex and abnormalities in synaptic transmission.[2,5,10]

Genetic factors may also influence the presence of seizures in DS, as the gene of progressive myoclonic epilepsy of Unverricht -Lundborg type and the gene determining subunit of glutamate receptors, both located on chromosome 21.[2,11]

All types of seizures may occur in patients with DS, although certain types are more frequent, with approximately 47% of patients developing partial seizures, 32% infantile spasms and 21% generalized tonic-clonic seizures. At younger ages, the most common types of seizures are infantile spasms and generalized tonic-clonic seizures, while at older ages, simple partial seizures, complex partial seizures and generalized tonic-clonic seizures.[2,5,10,11]

The classification of epilepsy among the patients with DS and epilepsy participating in this study (*GROUP I*) was the following: 5(14.7%) West syndrome (WS), 15(44.1%) focal epilepsy, 4(11.7%) multifocal epilepsy and 10(29.4%) generalized epilepsy. Our data are similar to those of other authors, with a predominance of focal epilepsies in children with DS.

However, our incidence of WS is lower than in other researches. The relationship between DS and infantile spasms does not seem to be merely casual, given the high number of reports of this association.[2,12,13] Other types of seizures reported in patients with DS are myoclonic seizures and the reflex epilepsies, more frequent in this group of people than in the general population.[2]

The EEG is a very useful method in the diagnosis and management of epilepsy[1]. Following the pattern of incidence of epilepsy described above, the incidence of electroencephalographic abnormalities in individuals with DS is significantly higher than in the general population, and lower than in other groups of patients with mental disabilities. Despite numerous studies on the subject, is not yet recognized a specific EEG pattern of the syndrome.[1,5]

Electroencephalographic abnormalities already described in people with DS are the following: spike, spike-wave complexes and polispike wave[1]. The detailed classification of epilepsy and EEG findings of patients participating in the study can be seen in Table 1.

In relation to thyroid dysfunction, its importance is clearly shown in the scientific literature about the subject, which demonstrates that 3-54% of these individuals have biochemical evidence of hypothyroidism with increased lifetime prevalence. Both hypothyroidism and hyperthyroidism are more common in people with DS than in the general population.[3,7,8]

Thyroid dysfunction in DS can be congenital or acquired, compensated (subclinical) or decompensated, transient or persistent, with hypothyroidism or hyperthyroidism.[3,9]

The most common form of thyroid dysfunction in these patients is transient subclinical hypothyroidism, which is characterized by slightly elevated levels of thyroid stimulating hormone (TSH) and normal levels of free-thyroxine (free-T4), with spontaneous lifetime recovery.[3,8,9]

Congenital hypothyroidism is up to 28 times more frequent in children with DS than in the general population.[3,7-9] This finding suggests that there may be genes on chromosome 21 involved in the development of the thyroid.[7,8] Some mechanisms proposed to explain thyroid dysfunction in these children are: thyroid relatively small (hypoplastic) in relation to age and the increased metabolic demands accompanying the body growth; dysfunction in the hypothalamic-pituitary-thyroid axis, delay in its maturation or slowness of response to TSH.[7-9,14,15] The acquired hypothyroidism is usually associated with the presence of antithyroid antibodies, suggesting an autoimmune etiology, being common occurrence from the age of 8 years, with an increase in incidence with advancing age.[3,9] It is known that the population with DS has increased prevalence of autoimmune diseases affecting both endocrine and non-endocrine organs, and the most common are those related to the thyroid gland, such as Hashimoto's thyroiditis. The antithyroid antibodies, Thyroid Peroxidase antibodies and Thyroglobulin antibodies are found in 13-34% of patients with DS, which may have normal thyroid function or have hypothyroidism or hyperthyroidism.[3,7]

It should be noticed that the clinical manifestations of DS in its natural course and hypothyroidism overlap in several aspects. For example, both may present hypotonia, lethargy, dullness, mental retardation, growth failure, prolonged jaundice neonatal, delayed closure of fontanellae, macroglossia, obesity etc.[3,7,9] Because of this, delay in diagnosis of hypothyroidism can occur in these people, leading to a deterioration in their health.[9]

The additive effects of DS and hypothyroidism undoubtedly can lead to amplification of health problems in this population.[9] An important example is growth failure.[7] Karlsson et al.[7] in their longitudinal study involving 85 children with DS demonstrated that the growth rate of children with DS and hypothyroidism is significantly lower than the growth rate of children with DS without hypothyroidism, with a significant improvement in this parameter after one year of treatment with levothyroxine.

Studies have found that even subclinical hypothyroidism can lead to the emergence of significant sequelae such as anemia, hypotonia and cognitive and growth deficits. Treatment with thyroid hormone replacement should be encouraged even in cases of subclinical hypothyroidism in view of the ease of its implementation in practice, virtually no adverse effects, and benefits in preventing the development of the aforementioned sequels and the evolution to a state of overt hypothyroidism.[3,7,8]

Hyperthyroidism is found less frequently than hypothyroidism in DS, without gender predominance. Its congenital form is rare, but its negative impacts on fetal and postnatal development require a more careful look at this condition.[9,16,17] In our study no cases of children with DS and hyperthyroidism were found.

There are several protocols for monitoring of thyroid hormones in patients with DS. Many authors suggest that patients with DS and normal thyroid function should be monitored annually, and those with subclinical hypothyroidism, every three months.[9]

In scientific literature, there are several reports of people with DS and thyroid dysfunction in association with other clinical conditions.[3] To date an association has been found between cases of DS and thyroid dysfunction with early puberty and diabetes *mellitus*.[3] In relation to thyroid dysfunction and epilepsy, despite its considerable prevalence and impact on health status of patients with DS, little is yet known.

It is well known that there is reciprocal influence between epilepsy and neuroendocrine system in the body. Hormonal changes may alter the excitability of neurons in the central nervous system (CNS), increasing the frequency of epileptic episodes and, on the other hand, these can alter the functioning of the neuroendocrine system, particularly the hypothalamus and pituitary. Studies in patients with epilepsy confirm that epileptic seizures alter circulating levels of endocrine hormones such as prolactin, luteinizing hormone (LH) and growth hormone (GH).[18]

In our study, in the group of children with DS and epilepsy, 67.65% patients were normal in relation to thyroid function and 32.35% had hypothyroidism, and no cases of hyperthyroidism were found. On the other hand, in the group of children with DS and without epilepsy, 84.21% were normal in relation to thyroid function and 15.8% had hypothyroidism, and no cases of hyperthyroidism were found. The statistical analysis shows no significant difference between the presence or absence of epilepsy and the presence or absence of hypothyroidism, and also no significant association between the mother's age at the child's birth and the increased risk of epilepsy and between the mother's age at the child's birth and the increased risk of hypothyroidism.

CONCLUSIONS

Therefore, our study found no significant association between the two comorbidities, epilepsy and thyroid dysfunctions, in people with DS, or significant relationship of each one individually with the mother's age at the child's birth in this population. This study aimed to contribute to the understanding of DS and its comorbidities, with focus on epilepsy and thyroid dysfunction. Although we found no association between these comorbidities in patients with DS, we emphasize to health professionals who deal with these people about the importance of early diagnosis and appropriate treatment of the comorbidities, so that this population has better health and quality of life. More studies are needed to elucidate the issues raised in this paper.

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WEST SYNDROME: ETIOLOGY AND EVOLUTION OF THE INTER-ICTAL EEG PATTERN IN A COHORT OF 24 PATIENTS

SÍNDROME DE WEST: ETIOLOGIA E EVOLUÇÃO DE PADRÃO INTERICTAL NO EEG EM UMA COORTE DE 24 PACIENTES

SÍNDROME DE WEST: ETIOLOGÍA Y EVOLUCIÓN DE ESTÁNDAR INTERICTAL EN EL EEG EN UNA COHORTE DE 24 PACIENTES

Natasha Santos Mata[1], Paulo Breno Noronha Liberalesso,[2] Jair Mendes Marques[2], Bianca Simone Zeigelboim[2], Eliana Garzon[3]

ABSTRACT

Objective: West syndrome (WS) is the most frequent epileptic encephalopathy in the first year of life. Diagnosis requires the presence of epileptic spasms, developmental delay, and hypsarrhythmia EEG pattern. Methods: A retrospective study on the etiology and evolution of inter-ictal electroencephalographic patterns in children with West syndrome referred to the Department of Pediatric Neurology at the Pequeno Príncipe Children's Hospital from January 2008 to January 2014. All children underwent magnetic resonance imaging and EEG. Results: Eighteen (75%) children had spasms, and 6 (25%) had spasms and tonic seizures. MRI scans showed agenesis of the corpus callosum (1/4.17%), dysplasia in the right frontal lobe (1/4.17%), dysplasia in the left frontal and parietal lobes (1/4.17%), pachygyria associated with agenesis of the corpus callosum (1/4.17%), periventricular nodes (2/8.33%), periventricular leukomalacia (3/12.5%), cerebral atrophy (3/12.5%), and multicystic encephalomalacia (6/25%). EEG monitoring showed hypsarrhythmia in the first exam in all cases; 18 (75%) progressed to multifocal epileptiform discharges (more than three independent epileptogenic foci), and 6 (25%) developed generalized spike-wave and polyspike-wave. Conclusions: Symptomatic form is the most common in WS and most patients develop multifocal epileptiform discharges visible in EEG.

Keywords: Spasms, infantile; Electroencephalography; Seizures.

RESUMO

Objetivo: A síndrome de West (SW) é a encefalopatia epiléptica mais frequente no primeiro ano de vida. O diagnóstico requer a presença de espasmos epilépticos, retardo de desenvolvimento e EEG com padrão de hipsarritmia. Métodos: Estudo retrospectivo sobre a etiologia e a evolução dos padrões eletroencefalográficos interictais em crianças com síndrome de West encaminhadas para o Departamento de Neurologia Pediátrica do Hospital Pequeno Príncipe, de janeiro de 2008 a janeiro de 2014. Todas as crianças foram submetidas a exames de ressonância magnética e EEG. Resultados: Dezoito crianças (75%) tinham espasmos e 6 (25%) tinham espasmos e convulsões tônicas. As imagens por RM mostraram agenesia do corpo caloso (1/4,17%), displasia no lobo frontal direito (1/4,17%), displasia nos lobos frontal esquerdo e parietal (1/4,17%), paquigiria associada à agenesia do corpo caloso (1/4,17%), nódulos periventriculares (2/8,33%), leucomalácia periventricular (3/12,5%), atrofia cerebral (3/12,5%) e encefalomalácia multicística (6/25%). A monitoração EEG mostrou hipsarritmia no primeiro exame em todos os casos; 18 (75%) progrediram para descargas epileptiformes multifocais (mais de três focos epileptogênicos independentes) e 6 (25%) evoluíram com espícula-onda e poliespícula-onda generalizadas. Conclusões: A forma sintomática é a mais comum na SW e a maioria dos pacientes desenvolve descargas epileptiformes multifocais aparentes no EEG.

Descritores: *Espasmos infantis; Eletroencefalografia; Convulsões.*

RESUMEN

Objetivo: El síndrome de West (SW) es la encefalopatía epiléptica más frecuente en el primer año de vida. El diagnóstico requiere la presencia de espasmos epilépticos, retardo de desarrollo y EEG con estándar de hipsarritmia. Métodos: Estudio retrospectivo sobre la etio-

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logía y la evolución de los estándares electroencefalográficos intericticales en niños con síndrome de West encaminados para el Departamento de Neurología Pediátrica del Hospital Infantil Pequeno Príncipe, desde enero de 2008 a enero de 2014. Todos los niños fueron sometidos a exámenes de resonancia magnética y EEG. Resultados: Dieciocho niños (75%) tenían espasmos y 6 (25%) tenían espasmos y convulsiones tónicas. Las imágenes por RM mostraron agenesia del cuerpo calloso (1/4,17%), displasia en el lóbulo frontal derecho (1/4,17%), displasia en los lóbulos frontal izquierdo y parietal (1/4,17%), paquigiria asociada a la agenesia del cuerpo calloso (1/4,17%), nódulos periventriculares (2/8,33%), leucomalacia periventricular (3/12,5%), atrofia cerebral (3/12,5%) y encefalomalacia multicística (6/25%). El monitoreo EEG mostró hipsarritmia en el primer examen en todos los casos; 18 (75%) avanzaron para descargas epileptiformes multifocales (más de tres focos epileptogénicos independientes) y 6 (25%) evolucionaron con espícula-onda y poliespícula-onda generalizadas. Conclusiones: La forma sintomática es la más común en la SW y la mayoría de los pacientes desarrolla descargas epileptiformes multifocales aparentes en el EEG.

Descriptores: *Espasmos infantiles; Electroencefalografía; Convulsiones.*

INTRODUCTION

West syndrome (WS) is the most frequent epileptic encephalopathy in the first year of life, with an incidence ranging between 2 and 3.5 / 10,000 live births, with a peak age of onset between three and seven months old.[1] This syndrome was originally described in 1841 in an article published in The Lancet, by an English physician named William James West in his own son, James Edwin West.[2]

Classically, for diagnosis the presence of (a) seizures classified as spasms (may be flexor, extensor or mixed), (b) a typical pattern in interictal electroencephalogram (EEG) denominated hypsarrhythmia and (c) developmental delay at diagnosis or during the course is required.[1]

Most cases of WS is classified as symptomatic and therefore related to structural or metabolic lesions of brain, especially malformations of cortical development, tuberous sclerosis, Aicardi and Down's syndrome, metabolic disorders, congenital infections, pre-natal hypoxia, among others. Less commonly, there are reports of cryptogenic cases in which neurological development that precedes the onset of symptoms is normal and the etiology is undetermined.[3]

Although hypsarrhythmia to be present in all patients with WS, this interictal pattern will always be replaced by another EEG pattern during the course of the disease. Thus, the main aim of this study is to analyze the evolution of EEG in a group of children with WS. All aspects of this research were approved by the Ethics Committee on Research Involving Human Subjects at our institution (number 771.087).

METHODS

This is a retrospective study about the etiology and evolution of interictal electroencephalographic patterns of WS children referred for the Department of Pediatric Neurology at the Pequeno Príncipe Children's Hospital from January/2008 to January/2014. Twenty-four patients were selected, 13 (54.17%) female and 11 (45.83%) male, all showing hypsarrhythmia pattern in the first EEG and with developmental delay at diagnosis.

Seizures were classified according to their clinical symptoms. All children were submitted to magnetic resonance imaging (MRI) and etiology was determined in almost all cases.

All EEG were performed for a minimum duration of 30 minutes, with electrodes positioned according to the International 10-20 System, in digital EEG monitoring equipments with 21 channels (Nihon Koden®, Neurotec® and Neurovirtual Brain Wave II®). EEG exams were performed sequentially until the hypsarrhythmia be replaced by another pattern and all exams were analyzed by the same physician.

RESULTS

In the group of 24 children included in the study, the age of seizures onset ranged from 5-15 months (mean 7.92 ± 2.52 months).

Etiology investigated by MRI

Eighteen (75%) children had exclusively spasms, and 6 (25%) had spasms and tonic seizures. The MRI was abnormal in 18 cases, showing agenesis of the corpus callosum (1/4.17%), dysplasia in the right frontal lobe (1/4.17%), dysplasia in the left frontal and parietal lobes (1/4.17%), pachygyria associated with agenesis of the corpus callosum (1/4.17%), periventricular nodes (2/8.33%), periventricular leukomalacia (3/12.5%), cerebral atrophy (3/12.5%), and multicystic encephalomalacia (6/25%). Six (25%) MRI scans of the brain were normal. Data from neuroimaging studies associated with clinical and / or neurological diagnosis history of each patient is shown in Table 1.

Evolution of interictal electroencephalographic patterns

All EEGs records showed hypsarrhythmia in the first examination, 18 (75%) progressed to multifocal epileptiform discharges (more than three independent epileptogenic foci) and six (25%) evolved with generalized spike-wave and polyspike-wave (Table 2). In none of the cases analyzed, did the EEG become normal after the disappearance of hypsarrhythmia.

DISCUSSION

In most cases, the parents bring the child to a pediatrician or pediatric neurologist because they realize the onset of spasms. Initially, these spasms can be confused with abdominal colic or gastroesophageal reflux. However, after a careful medical history and a detailed neurological examination, the diagnosis of WS is relatively simple. The spasms can occur alone or associated with other types of seizures, especially generalized tonic seizures. Epileptic spasms can be classified into flexors, extensors and mixed (combination of both earlier), depending on the muscle groups involved, and generally predominate in moments of transition from wakefulness to drowsiness or upon awakening. The spasms are clinically characterized by sudden and rapid contractions of muscle groups of the neck, arms and thighs. Simultaneously, the eyes may have tonic upward deflection. The contraction is often followed by a cry. Sometimes, mainly in patients treated with antiepileptic drugs, spasms can occur only with deviation of the eyes upward. These seizures typically occur clustered and have very variable frequency, occurring a few times to hundreds of times a day.[4] In our study, all patients had developmental delay at diagnosis of WS. Most of our patients had only spasms. Only a third had spasms associated with tonic seizures.

Table 1. Magnetic resonance of brain and relationship with clinical history or neurological diagnosis.

P	Scans	Historical clinical / neurological diagnosis
1	Multicystic encephalomalacia	Hypoxic-ischemic injury in childbirth
2	Normal	Down syndrome
3	Right frontal dysplasia	Brain malformation
4	Agenesis of the corpus callosum	Brain malformation
5	Multicystic encephalomalacia	Hypoxic-ischemic injury in childbirth
6	Brain atrophy	Hypoxic-ischemic injury in childbirth
7	Normal	Down syndrome
8	Brain atrophy	Hypoxic-ischemic injury in childbirth
9	Multicystic encephalomalacia	Hypoxic-ischemic injury in childbirth
10	Normal	No clinical history of neurological diseases
11	Dysplasia frontal and parietal (left)	Brain malformation
12	Multicystic encephalomalacia	Hypoxic-ischemic injury in childbirth
13	Normal	Down syndrome
14	Periventricular leukomalacia	Prematurity
15	Normal	Down syndrome
16	Periventricular leukomalacia	Prematurity
17	Multicystic encephalomalacia	Hypoxic-ischemic injury in childbirth
18	Periventricular leukomalacia	Prematurity
19	Brain atrophy	Hypoxic-ischemic injury in childbirth
20	Normal	No clinical history of neurological diseases
21	Pachygiria and agenesis of the corpus callosum	Brain malformation
22	Multicystic encephalomalacia	Hypoxic-ischemic injury in childbirth
23	Periventricular nodules	Tuberous sclerosis
24	Periventricular nodules	Tuberous sclerosis

P=Patient

Etiology

The causes of WS appear to be extremely variable and its pathophysiology is not completely known. It is possible that in all patients with WS there is an increase in the release of stress -activated mediators in the brain (particularly the neuropeptide CRH) in the limbic and brain stem regions.[5] A malfunction in the regulation of the GABA transmission process may also occur in some cases.[6]

The WS can be classified as cryptogenic or probably symptomatic (etiology cannot be clearly determined) and a symptomatic form (etiology is clearly defined). There is controversy about the existence of an idiopathic form. A Brazilian study of 95 children with WS (62% male) with mean age of 4.9 (±5.0), concluded that 72.6% were symptomatic, 26.3% were cryptogenic and only 1.1% were idiopathic.[7]

Pre-natal asphyxia is a very frequent cause of WS in countries where care during pregnancy is inadequate.[8] Therefore, pregnancy and pre-natal complications are often related to WS in many regions of Brazil.

Brain lesions are present in 60-90 % of all children with WS, and almost half of these patients have radiological signs of cerebral atrophy. MRI has a high capacity to identify small cortical and subcortical lesions and should be performed in all cases. Brain malformations are identified in at least one third of patients with WS, including focal cortical dysplasia, polymicrogyria, pachygyria, schizencephaly, lissencephaly, and agenesis or dysgenesis of the corpus callosum, subcortical band heterotopias and double cortex syndrome.[8,9]

Patients with neuromesoectodermosis or neurocutaneous syndromes, particularly tuberous sclerosis, may also evolve with WS.[8] When the WS occurs in children with tuberous sclerosis, the evolution seems to be more benign.[10]

WS may also occur in children with genetic syndromes. It is considered one of the most frequent generalized epileptic

Table 2. Evolution of interictal electroencephalographic patterns in West syndrome.

Patient	EEG 1	EEG2	EEG 3	EEG 4	EEG 5	EEG 6
1	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---
2	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---
3	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---
4	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	G-SW/PSW	---
5	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	G-SW/PSW
6	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	G-SW/PSW	---	---
7	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	Multifocal SW	---	---
8	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW
9	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	G-SW/PSW.	---	---
10	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---
11	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---	---	---
21	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW
13	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	G-SW/PSW	---	---
14	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---
15	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW
16	Hypsarrhythmia	Multifocal SW	---	---	---	---
17	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW
18	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---	---
19	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---
20	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	Multifocal SW	---
21	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---
22	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---	---	---
23	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Multifocal SW	---	---
24	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	G-SW/PSW	---	---

SW – sharp wave. G-SW/PSW – generalized spike-wave and polyspike-wave.

encephalopathies in children with Down's syndrome (DS). The mechanisms that explain the high incidence of epilepsy in DS are not completely known. However, structural brain abnormalities, persistent fetal dendritic morphology, underdeveloped synaptic profiles and high concentrations of carbonic anhydrase II occur in many individuals with epilepsy, WS and DS.[8,11,12]

Recently, two genes located in the human chromosome Xp22 region (ARX and CDKL5), have been found to be responsible for cryptogenic WS.[8,9]

Similarly to the medical literature,[8] most of our patients (75%) had some changes in MRI being classified as a symptomatic form of WS. In half of our cases the brain damage (cerebral atrophy or multicystic encephalomalacia) was caused by complications and hypoxic-ischemic injury in childbirth. Pre-maturity and periventricular leukomalacia are infrequent causes of WS. However, we found three cases in our study. As observed in other authors,[8,10,12] DS and tuberous sclerosis were frequent causes of WS in our patients, occurring in one third of cases.

Evolution of interictal electroencephalographic patterns

The presence of hypsarrhythmia is required for the diagnosis of the syndrome. The hypsarrhythmia was described by F.A. Gibbs and E.L. Gibbs consists of "random high-voltage slow waves and spikes, that vary from time to time, both in location and duration. At times they appear to be focal, and a few seconds later they seem to originate from multiple foci. Occasionally, the spike discharge becomes generalized, but it never appears as a rhythmically repetitive and highly organized pattern that could be confused with a discharge of the *petit mal* variant type".[13]

Early in the disease, the hypsarrhythmia may be interspersed with periods of normal brain electrical activity. However, after a period of days or a few weeks, the hypsarrhythmia becomes constant in the EEG during wakefulness and sleep. This abnormal EEG activity is continuous and chaotic, but in sleep it can be fragmented. Several authors have described atypical hypsarrhythmia, also called modified hypsarrhythmia, including forms with increased interhemispheric synchronization, with a consistent focus of abnormal discharge, asymmetrical hypsarrhythmia, patterns with hypsarrhythmia with episodes of attenuation and forms with hypsarrhythmia comprising mainly high voltage slow activity (with little amount of spiky activity).[14] The hypsarrhythmia is usually easily recognized and this is very important because it has implications for the choice of the most appropriate antiepileptic drug. In our group of patients, all children had the hypsarrhythmia in classic form in the first EEG.

In our series, all patients showed the classic form of hypsarrhythmia. The hypsarrhythmia is an age-dependent EEG abnormality. Therefore after a few months or years it is always replaced by another pattern in the EEG.

There are few studies reporting on the evolution of interictal patterns in WS.

The classic studies of Gibbs et al.[15] showed that 75% of children with WS remained with focal discharges after the disappearance of hypsarrhythmia and this data corresponds exactly to what we found in our study.

In idiopathic WS would be possible that the EEG evolved to normality after the disappearance of hypsarrhythmia.[7] However, this form is considered very rare and was not observed in our study.

CONCLUSIONS

Our data show that most children with WS are classified as symptomatic forms (brain injury may be seen in scans) and that most also evolve with multifocal epileptiform discharges. Although WS has been analysed for over a century and a half, questions remain about its pathophysiology. Furthermore, it remains the most common form of epileptic encephalopathy in the first year of life, justifying further research on this topic.

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BENIGN PARTIAL EPILEPSY OF CHILDHOOD WITH CENTROTEMPORAL SPIKES AND SLEEP DISORDERS

EPILEPSIA PARCIAL BENIGNA DA INFÂNCIA COM ESPÍCULA CENTROTEMPORAL E TRANSTORNOS DO SONO

EPILEPSIA PARCIAL BENIGNA DE LA INFANCIA CON ESPÍCULA CENTROTEMPORAL Y TRASTORNOS DEL SUEÑO

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ABSTRACT

Objective: Benign partial epilepsy of childhood with centrotemporal spikes (BECTS) is an idiopathic epilepsy that occurs in healthy children with normal neurodevelopment, characterized by seizures and inter-ictal discharges that predominate during nighttime sleep. This research analyzes the prevalence of sleep disorders in patients with BECTS followed in the Department of Pediatric Neurology at the Pequeno Príncipe Children's Hospital from January 2004 to January 2014. Methods: This study is observational and cross-sectional. The medical records of all children with BECTS followed in the aforementioned institution and period were analyzed, and 46 of these patients met the prerequisites to enter the study. During the investigation all children underwent neuroimaging exams (magnetic resonance or computed tomography) and digital electroencephalogram. In clinical evaluations, all patients and their parents were asked about the presence of sleep disorders. Results: To be classified as having BECTS, patients should have normal neural images and all the electroencephalographies (EEG) should have normal background activity with unilateral or bilateral spikes in centrotemporal or centrotemporal and parietal regions. All were being treated with antiepileptic drugs. The age of onset of seizures ranged from 62 to 145 months (mean 94.37 ± 21.2 months). Data showed that 33 (71.74%) out of 46 patients had experienced some kind of sleep disorder: insomnia (18 patients/39.13%), nocturnal enuresis (6 patients/13.04%), somnambulism (2 patients/4.35%), night terrors (1 patient/2.17%), nocturnal enuresis and night terrors (2 patients/4.35%), night terrors and somnambulism (2 patients/4.35%), insomnia and nocturnal enuresis (1 patient/2.17%) and insomnia, night terrors and somnambulism (1 patient/2.17%). Conclusions: Most children diagnosed with BECTS in our pediatric neurology service presented with comorbid sleep disorder. The results are consistent with the data collected in the literature, which show that sleep disorders are more common in children with this type of epilepsy than in those neurologically healthy.

Keywords: Sleep disorders; Epilepsies, partial; Neurology.

RESUMO

Objetivo: A epilepsia parcial benigna da infância com espículas centrotemporais (EPCT) é uma epilepsia idiopática que ocorre em crianças saudáveis com neurodesenvolvimento normal, que se caracteriza por convulsões e descargas interictais que predominam durante o sono noturno. Esta pesquisa analisa a prevalência de transtornos do sono em pacientes com EPCT acompanhados no Departamento de Neurologia Pediátrica do Hospital Infantil Pequeno Príncipe de janeiro de 2004 a janeiro de 2014. Métodos: Este estudo é observacional e transversal. O prontuário clínico de todas as crianças com EPCT acompanhadas na instituição e no período acima mencionados foi analisado e 46 desses pacientes satisfizeram os pré-requisitos para entrar no estudo. Durante a investigação, todas as crianças foram submetidas a exames de neuroimagem (ressonância magnética ou tomografia computadorizada) e a eletroencefalograma digital. Durante as avaliações clínicas, todos os pacientes e seus pais foram perguntados sobre a presença de transtornos do sono. Resultados: Para serem classificados como portadores de EPCT, os pacientes deviam ter imagens neurais normais e todas as eletroencefalografias (EEG) deviam apresentar atividade de fundo normal, com espículas unilaterais ou bilaterais nas regiões centrotemporal ou centrotemporal e parietal. Todos estavam sendo tratados com medicação

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antiepiléptica. A idade de início das convulsões variou dos 62 aos 145 meses (média 94,37 ± 21,2 meses). Os dados mostraram que 33 (71,74%) dos 46 pacientes tinham algum tipo de transtorno do sono: insônia (18 pacientes/39,13%), enurese noturna (6 pacientes/13,04%), sonambulismo (2 pacientes/4,35%), terrores noturnos (1 paciente/2,17%), enurese noturna e terrores noturnos (2 pacientes/4,35%), terrores noturnos e sonambulismo (2 pacientes/4,35%), insônia e enurese noturna (1 paciente/2,17%) e insônia, terrores noturnos e sonambulismo (1 paciente/2,17%). Conclusões: A maioria das crianças com diagnóstico de EPCT em nosso serviço de neurologia pediátrica apresentou-se com transtornos do sono comórbidos. Os resultados são compatíveis com os dados coletados na literatura, que mostram que os transtornos do sono são mais comuns em crianças com esse tipo de epilepsia do que nas neurologicamente saudáveis.

Descritores: *Transtornos do sono; Epilepsias parciais; Neurologia.*

RESUMEN

Objetivo: La epilepsia parcial benigna de la infancia con espículas centrotemporales (EPCT) es una epilepsia idiopática que ocurre en niños saludables con neurodesarrollo normal, que se caracteriza por convulsiones y descargas interictales que predominan durante el sueño nocturno. Esta investigación analiza la prevalencia de trastornos del sueño en pacientes con BECTS acompañados en el Departamento de Neurología Pediátrica del Hospital Pequeno Príncipe desde enero de 2004 a enero de 2014. Métodos: Este estudio es observacional y transversal. El prontuario clínico de todos los niños con EPCT acompañados en la institución y en el período arriba mencionado fue analizado y 46 de esos pacientes cumplieron con los prerrequisitos para entrar en el estudio. Durante la investigación, todos los niños fueron sometidos a exámenes de neuroimagen (resonancia magnética o tomografía computada) y a electroencefalograma digital. Durante las evaluaciones clínicas, todos los pacientes y sus padres fueron preguntados sobre la presencia de trastornos del sueño. Resultados: Para ser clasificados como portadores de EPCT, los pacientes debían tener imágenes neurales normales y todas las electroencefalografías (EEG) debían presentar actividade de fondo normal, con espículas unilaterales o bilaterales en las regiones centrotemporal o centrotemporal y parietal. Todos estaban siendo tratados con medicación antiepiléptica. La edad de inicio de las convulsiones varió de los 62 a los 145 meses (promedio de 94,37 ± 21,2 meses). Los datos mostraron que 33 (71,74%) de los 46 pacientes tenían algún tipo de trastorno del sueño: insomnia (18 pacientes/39,13%), enuresis nocturna (6 pacientes/13,04%), sonambulismo (2 pacientes/4,35%), terrores nocturnos (1 paciente/2,17%), enuresis nocturna y terrores nocturnos (2 pacientes/4,35%), terrores nocturnos y sonambulismo (2 pacientes/4,35%), insomnia y enuresis nocturna (1 paciente/2,17%) e insomnia, terrores nocturnos y sonambulismo (1 paciente/2,17%). Conclusiones: La mayoría de los niños con diagnóstico de EPCT en nuestro servicio de neurología pediátrica se presentó con trastornos del sueño comórbidos. Los resultados son compatibles con los datos colectados en la literatura, que muestran que los trastornos del sueño son más comunes en niños con ese tipo de epilepsia que en los neurológicamente saludables.

Descriptores*: Trastornos del sueño; Epilepsias parciales; Neurología .*

INTRODUCTION

Benign partial epilepsy of childhood with centrotemporal spikes (BECTS), also known as benign rolandic epilepsy or benign rolandic epilepsy of childhood, is placed among the idiopathic localization-related epilepsy. It is one of the most common epilepsy in children. BECTS is an idiopathic epilepsy that occurs in healthy children with normal neurodevelopment. The seizures are usually partial, with motor manifestation, and are more frequent during nighttime sleep. They often begin on face (patients usually have a feeling of tingling on one side of their mouth, tongue, lips, gum and cheek) and then progress to the arm and leg on the same side of the body. During the seizure the speech can be impaired. The evolution to generalized seizures (generalized tonic-clonic seizure) is relatively common, especially in younger children.

Some epilepsies are closely associated with sleep, such as awakening grand mal, juvenile myoclonic epilepsy, childhood epilepsy with occipital paroxysm, autosomal dominant frontal lobe epilepsy, Landau-Kleffner syndrome and BECTS. Specifically in BECTS, discharges are intensely activated by sleep.

Although ineffective sleep is common in epilepsy patients, how epilepsy or the epileptic discharges affect sleep is not yet completely know. One of the most accepted theories is that nocturnal seizures can disrupt the neurophysiology of sleep, producing sleep fragmentation, suppression of REM sleep and increased spontaneous arousals. Cortesi et al.[1] showed that children with idiopathic epilepsy had more sleep disturbances than neurologically healthy children, and these sleep disturbances were associate with seizure frequency, paroxysmal activity on EEG, duration of epilepsy and behavioral problems.

Even though seizures increase the incidence of sleep disorders in children, the administration of antiepileptic drugs (AED) can also significantly alter the physiology of sleep.

As well as seizures may affect quality of sleep, it is also known that sleep deprivation and sleep disorders both increase the incidence of seizures in epileptic patients, making the interrelationship between epilepsy and sleep extremely complex.

Children with insomnia may have more daytime fatigue, anxiety, mood oscillations and lower ability to complete tasks. Studies show that school performance can be also impaired. Being aware that all mentioned above could cause negative impact on these patients quality of life enhance the importance of studying the relationship between sleep and seizures.

This research aims to analyze the prevalence of sleep disorders in patients with BECTS referred for the Department of Pediatric Neurology at the Pequeno Príncipe Hospital from January/2004 to January/2014. All aspects of this project were approved by the Ethics Committee on Research Involving Human Subjects at our institution (number 801.103/2014).

METHODS

This study is observational and cross-sectional. All medical records of a cohort of patients with BECTS referred for the Department of Pediatric Neurology at the Pequeno Príncipe Children's Hospital from January/2004 to January/2014 were

analyzed, an data concerned the prevalence of sleep disorders were collected.

To be part of this research the patient should have: (a) normal development skills, (b) at least one normal neuroimaging exam (magnetic resonance imaging – MRI, or computed tomography - CT) and (c) one electroencephalogram recorded for at least 30 minutes, with electrodes positioned according to the International 10-20 System, in digital EEG monitoring equipments with 21 channels (Nihon Koden®, Neurotec® and Neurovirtual Brain Wave II®), analyzed by the same physician, with results suggesting BECTS.

Forty-six patients fit all the requirements to be part of this study and were selected, 24 (52.17%) of them female and 22 (47.83%) of them male. All patients and parents had been asked about the presence of sleep disorders during medical evaluations, and this was the data collected from the medical records.

RESULTS

The age of seizures onset on the group ranged from 62 to 145 months old (mean 94.37 ± 21.2). The patient's age at the time of inclusion in the study ranged from 74 to 165 months old (mean 118.8±27.08). All patients were submitted to a neuroimaging exam, 27 of them had an MRI performed and 19 patients had a CT Scan. All these neuroimaging exams were analyzed and classified by a radiologist as normal.

All patients were also submitted to an electroencephalogram. The results were analyzed by the same physician and all of them had normal background activity with sharp waves on the centrotemporal or centrotemporal and parietal regions, uni or bilateral. These results are compatible with BECTS.

Data showed that 33 out of 46 patients (71.74%) had experienced any sleep disorder after being diagnosed with BECTS: 18 patients (39.13%) mentioned to have experienced insomnia, 6 patients (13.04%) had nocturnal enuresis, 2 patients (4.35%) had somnambulism, 1 patient (2.17%) suffered from night terror, 2 patients (4.35%) had both nocturnal enuresis and night terrors, 2 patients (4.35%) had both night terrors and somnambulism, 1 patient (2.17%) had both insomnia and nocturnal enuresis and 1 patient (2.17%) mentioned to have insomnia, night terrors and somnambulism.

All 46 patients were being treated with antiepileptic drugs: 18 of them were on oxcarbazepine (39.13%), 17 carbamazepine (36.95%), four on sodium valproate (8.70%), tree on carbamazepine and clonazepam (6.52%), two on sodium valproate and clobazam (4.35%), oneon carbamazepine and clobazam (2.17%), and one on oxcarbazepine and clonazepam (2.17%). The patient's age at the first seizure and the results of the EEG performed are shown in Table 1.

Table 1. Electroencephalographic tests and age at first seizure.

Patient	First Seizure	Electroencephalogram
1	84	Normal background. SW C-P right and left
2	75	Normal background. SW C-P-T right and left
3	70	Normal background. SW C-P-T right
4	71	Normal background. SW C-P right
5	90	Normal background. SW C-P right and left
6	79	Normal background. SW C-P-T left
7	85	Normal background. SW C-P-T left
8	80	Normal background. SW C-P left
9	68	Normal background. SW C-P right
10	74	Normal background. SW C-P right
11	81	Normal background. SW C-P right
12	102	Normal background. SW C-P-T left
13	96	Normal background. SW C-P right
14	68	Normal background. SW C-P-T right and left
15	107	Normal background. SW C-P-T right and left
16	102	Normal background. SW C-P-T right and left
17	81	Normal background. SW C-P right
18	84	Normal background. SW C-P right and left
19	93	Normal background. SW C-P right
20	102	Normal background. SW C-P right and left
21	80	Normal background. SW C-P right and left
22	76	Normal background. SW C-P right
23	67	Normal background. SW C-P left
24	109	Normal background. SW C-P right and left
25	117	Normal background. SW C-P-T right and left
26	79	Normal background. SW C-P-T right and left
27	101	Normal background. SW C-P-T right
28	94	Normal background. SW C-P right
29	99	Normal background. SW C-P right and left
30	93	Normal background. SW C-P-T right
31	110	Normal background. SW C-P-T right and left
32	123	Normal background. SW C-P left
33	141	Normal background. SW C-P-T left
34	78	Normal background. SW C-P left
35	89	Normal background. SW C-P right
36	62	Normal background. SW C-P-T right and left
37	112	Normal background. SW C-P right and left
38	143	Normal background. SW C-P right
39	132	Normal background. SW C-P-T right and left
40	102	Normal background. SW C-P right
41	87	Normal background. SW C-P left
42	89	Normal background. SW C-P right
43	92	Normal background. SW C-P left
44	93	Normal background. SW C-P-T left
45	136	Normal background. SW C-P right and left
46	145	Normal background. SW C-P-T right and left

SW - sharp wave; C - central; P - parietal; T - temporal.

DISCUSSION

The neurophysiological bases of sleep were unknown until the XX middle century. From that moment ahead, several researches showed that sleep results of the complex interaction between innumerous endogenous and exogenous factors. The most known endogenous factors are levels of excitatory and inhibitory neurotransmitters (such as acetylcholine, norepinephrine, histamine, dopamine and hypocretin), the levels of hormones and the integrity of several cortical and subcortical structures (such as the ascending reticular activating system, the hypothalamus and the pineal gland).[2] The most known exogenous factors are ambient temperature, overeating at night, light intensity and noise level.

If all these endogenous and exogenous factors interact harmoniously, the neurologically healthy children should have a predominant nocturnal sleep and maintain wakefulness during the day.[2] Any condition that causes functional or structural changes in brain structures or in the biochemical system of sleep will probably result in changes on the normal pattern of sleep, called sleep disorders.

The electrographic record of sleep, made with the polysomnography, is used to classify and divide sleep in two main stages: NREM (non-rapid eyes movement) and REM (rapid eyes movement). The NREM stage can be subdivided into light (stages I and II) and deep (stage III and IV). Although the physiologic basis of this phenomenon is poorly understood, seizures and interictal epileptic discharges are more frequent during NREM sleep (mainly in stages I and II). Seizures are rare during REM sleep, when the incidence of interictal epileptic discharge also decreases significantly. This can probably be explained by the activation of the thalamocortial rhythms during NREM sleep.[3]

Antiepileptic drugs

The use of Antiepileptic drugs (AED) is an important aspect to be considered when analyzing sleep disorders and epilepsy. Many AED are known to cause significantly sleep interference in children with epilepsy, but relationship between AED and sleep disorder is not fully known. Each drug has it's personal sleep effect: tiagabine, levetiracetam and pregabalin increase sleep stage III; topiramate decreases sleep latency; lamotrigine increases both sleep stage II and REM and decreases sleep stage III; gabapentin increases both sleep stage III and REM; ethosuximide increases sleep stage I and decreases sleep stage III; valproate increases sleep stage I and decreases sleep stage II; phenytoin increases both sleep stages I and II and decreases sleep stage III; phenobarbital increases sleep stage II and decreases REM. Carbamazepine and oxcarbamazepine almost do not affect both NREM and REM sleep. Some AED like ethosuximide, primidone, felbamate, fosphenytoin, lamotrigine, topiramate and zonisamidedo still do not have clinical effects on sleep completely known.[4]

Besides the effects on proper sleep, all AED can cause sedation depending on the dose used, which can interfere in daytime wakefulness and productivity. They can also cause impairment of cognitive performance, being phenobarbital the one that affects the most, followed by phenytoin, benzodiazepines, carbamazepine and valproate.

In our study all patients were treated with at lest one AED. As BECTS is an idiopathic focal epilepsy, 40 (86,96%) of our patients were treated with carbamazepine or oxcarbazepine (with or without association of benzodiazepines). Only 6 (13,04%) of our patients were treated with sodium valproate (with or without association with benzodiazepines). As the study was observational and cross-sectional it was not possible to evaluate if the AED used on each patient had any relation with the presence of sleep disorders.

Insomnia

According to the Brazilian Society of Sleep, insomnia is defined as a difficulty to initiate or maintain sleep, provoking an impairment in daytime activities performance.[5] It is a disease of high prevalence in the general population. Epidemiological studies have shown a prevalence of 35.4% in Brazil,[6] 17.7% in France.[7] 20% in Switzerland,[8] and 31% in Germany, but none of these studies specified the prevalence on specifics pediatrics populations.[9] Data about the prevalence of insomnia in children vary a lot according to different researches and different countries making the analysis of these data complicated.

Insomnia disorders are most often classified as either primary or secondary to psychiatric or other medical conditions. The main causes of insomnia in childhood and adolescence are overeating at night, cow's milk protein allergy, chronic diseases, fear, anxiety, other emotional disturbances and misguided family's orientation. Children with insomnia may experience more daytime fatigue, anxiety, mood oscillations and have lower ability to complete tasks.[10] Studies show that school performance may also be impaired.

Our data show that 43.48% of the children with BECTS treated at our hospital also had insomnia. This is compatible with data found in literature that shows that the prevalence of insomnia in patients with BECTS is considerably higher than in healthy individuals.

Nocturnal enuresis

Nocturnal enuresis (NE) is the most common disorder of childhood sleep and may occur during either NREM or REM sleep. There are different definitions for NE, however the main concept of this condition may be understood as urinary incontinence during sleep after the usual age of urinary continence acquisition. The diagnostic criteria are: (a) chronological age higher than 5 years old; (b) mental age higher than 4 years old; (c) absence of any organic disease that may be associated with incontinence; (d) two or more monthly events of urinary incontinence for children aged between 5 and 6 years old, or one or more monthly events for children over 6 years old.[10]

Norgaard et al.[11] suggest to classify nocturnal enuresis as (a) primary - children who have never had urinary continence; (b) secondary - enuresis begins after a period of at least six months of urinary incontinence; (c) familial - at least one parent has a history of nocturnal enuresis; (d) polyuric - excessive production of urine overnight. The prevalence varies considerably, but stands around 10% on 7 years old children.[12]

The etiology of nocturnal enuresis is still unknown and is most likely multifactorial. Probably this disease is related to genetic, psychological, social and anatomo-physiological (bladder size, reactivity abnormal or/and lack of vasopressin release during sleep) factors. Another contributor factor may be an immaturity of the thalamus, which could impair awakening during the night, causing the NE. However the causes of NE still remain unknown.[13,14]

Our data show that 19.56% of the children with BECTS treated at our hospital were also diagnosed with NE. This prevalence is higher than that found in non-epileptic children[12] goes along with data found on literature.

Night terrors

Night terrors (NT) is the most dramatic sleep-arousal disorder. It is a NREM sleep-arousal parasomnia that occurs from childhood to adolescence. Its prevalence varies between 1% to 5% on this age group population. The events typically begin with intense agitation followed by crying, screaming and eye opening. The patients become tachycardic, diaphoretic and mydriatic. They are inconsolable and their behavior may become violent and result in injury to themselves and others. The children usually do not remember the episode on the day after. To differentiate night terror from seizures is relatively simple: unlike seizures, after a night terror episode the consciousness recovery is always fast and complete.[10]

Our data show that 13.04% of the children with BECTS treated at our hospital were also diagnosed with NT. This prevalence is significantly higher than that reported in other studies made in healthy general population[10] e goes along with data found on literature.

Somnambulism

Somnambulism is a NREM sleep-arousal parasomnia characterized by simple or complex motor phenomena during sleep. It begins during slow wave sleep. The patient can get out of bed, walk short distances, manipulate objects, urinate, eat and talk. Less often, they may experience psychomotor agitation, tachycardia, diaphoresis and aggressive reactions (rarely). As the motor functions are active while the child is still unconscious, they do not remember anything on the next morning.[10] Somnambulism is more common in childhood (the highest incidence is between 11 to 12 years old) than in adults. Different studies show it's prevalence in healthy children between 1 and 17%.[15,16]

Our data show that 10.87% of the children with BECTS treated at our hospital were also diagnosed with somnambulism.

This prevalence is similar to the prevalence found on literature on children without epilepsy.

CONCLUSION

The data from this study show that most children diagnosed with BECTS attended in our pediatric neurology service had comorbid some sleep disorder. This is consistent to data found at literature about sleep disorders and epilepsy. Insomnia, NE and NT were more frequent in our BECTS patients than in the healthy general population. Only the prevalence of somnambulism was similar among patients with BECTS and healthy individuals.

Although it is evident that children with specific types of epilepsy have worse quality of sleep, how epilepsy or epileptic discharges alter the macro and microstructure of sleep is still poorly understood. When mistreated, sleep disorders have a negative impact on these patients quality of life, causing children to have more daytime fatigue, anxiety, mood oscillations and lower ability to complete tasks. School performance can also be impaired. Despite being more frequent in children with epilepsy than in healthy ones, the spontaneous emergence of sleep complaint is not frequent during routine evaluation of these children.[10] leaving to the physician the responsibility of the diagnose.

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Review Article/Artigo de Revisão/Artículo de Revisión

TEMPORAL STEM ANATOMY APPLIED TO EPILEPSY SURGERY

ANATOMIA DO TRONCO TEMPORAL APLICADA À EPILEPSIA

ANATOMÍA DEL TRONCO TEMPORAL APLICADA A LA EPILEPSIA

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ABSTRACT

This study aims to provide a brief anatomical review of the temporal stem and its white matter fiber tracts related to temporal lobe epilepsy (TLE) surgery, and review the tractography strategies to access these white matter fiber tracts using Diffusion Tensor Image (DTI) techniques. The pertinent literature about the temporal stem anatomy and function was reviewed. DTI techniques used at our neuroimaging facility were presented, as well as the tractography strategies to find the main white matter tracts coursing through the temporal stem. The knowledge of the temporal stem anatomy and the DTI techniques are important tools to analyze the white matter fiber tracts involved in TLE surgery. Such analysis is considered to be important for further evaluating the clinical role of TS and its preservation as well as to propose more selective approaches to TLE.

Keywords: Epilepsy; Amygdala; Anatomy; Magnetic resonance imaging.

RESUMO

Este estudo tem por objetivo proporcionar uma breve revisão anatômica do tronco temporal e dos tratos de fibras de substância branca relacionados com a cirurgia da epilepsia do lobo temporal (ELT) e revisar as estratégias de tractografia para ter acesso a esses tratos de fibras de substância branca usando técnicas de imagem de tensor de difusão (ITD). A literatura pertinente sobre a anatomia do tronco temporal e sua função foi analisada. As técnicas de ITD usadas em nossas instalações de neuroimagem foram apresentadas, assim como as estratégias de tractografia para encontrar os principais tratos de substância branca que fazem trajeto através do tronco temporal. O conhecimento da anatomia do tronco temporal e as técnicas de ITD são ferramentas importantes para analisar os tratos de fibras de substância branca envolvidos na cirurgia da ELT. Essa análise é considerada importante para melhor avaliar o papel clínico do tronco temporal e sua preservação, bem como para propor abordagens mais seletivas para a ELT.

Descritores: *Epilepsia; Tonsila do Cerebelo; Anatomia; Imagem por Ressonância Magnética.*

RESUMEN

Este estudio tiene por objetivo proporcionar una breve revisión anatómica del tronco temporal y de los tractos de fibras de sustancia blanca relacionados con la cirugía de la epilepsia del lóbulo temporal (ELT) y revisar las estrategias de tractografía para tener acceso a esos tractos de fibras de sustancia blanca usando técnicas de imagen de tensor de difusión (ITD). Fue analizada la literatura pertinente sobre la anatomía del tronco temporal y su función. Fueron presentadas las técnicas de ITD usadas en nuestras instalaciones de neuroimagen, así como las estrategias de tractografía para encontrar los principales tractos de sustancia blanca que hacen el trayecto a través del tronco temporal. El conocimiento de la anatomía del tronco temporal y las técnicas de ITD son herramientas importantes para analizar los tractos de fibras de sustancia blanca involucrados en la cirugía de ELT. Ese análisis es considerado importante para evaluar mejor el papel clínico del tronco temporal y su preservación, bien como para proponer abordajes más selectivos para la ELT.

Descriptores: *Epilepsia; Amígdala del cerebelo; Anatomía; Imagen por resonancia magnética.*

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INTRODUCTION

Temporal Lobe Epilepsy (TLE) is the most common epileptic syndrome refractory to clinical treatment.[1] The surgical resection of the hippocampus and amygdala remains as the treatment of choice to refractory cases.[2,3] Selective and non-selective approaches were proposed but controversy remains related to both selectivity and seizure controlling advantages comparing different approaches.[4]

Within the white matter fiber tracts studies of Ture[5] and the evolution of neuroradiological image, especially Diffusion Tensor Image (DTI), great concern about the importance of the uncinate fasciculus, the Meyer's loop and the inferior fronto-occipital fasciculus, among others, was taken into account, as many of these white matter fiber tracts are at potential risk of injury in TLE surgery.

In this paper, anatomical review of the temporal stem and its white matter fiber tracts related to TLE surgery was performed. We also reviewed the tractography strategies to get these white matter fiber tracts using new DTI techniques.

MATERIAL AND METHODS

Literature review was performed on the Pubmed Database using all combinations of the following key-words: 'temporal stem, 'epilepsy surgery', 'diffusion tensor image', and 'white matter fiber tracts'. Emphasis was placed on anatomical and radiological articles, with English-language. Two investigators screening the pertinent abstracts (EG and AFJ) identified the potential papers for inclusion, based on the purpose of our review – the discussion of the white matter tracts of the temporal stem in epilepsy surgery as well as their neuroradiological evaluation.

The volunteers included in this study signed informed consent, approved by the Ethics Committee of the Faculty of Medical Sciences of the University of Campinas. MRI data were acquired on a 3T Philips Achieva (Best, The Netherlands) at the University Hospital at the University of Campinas in São Paulo state, Brazil. The scan protocol was based on a T1-weighted image with isotropic voxels of 1 mm, acquired in the sagittal plane, 1 mm thick, no gap, flip angle=8°, TR=7.0 ms, TE=3.2 ms, matrix=240x240, FOV=240x240 and in a DTI (2x2x2 mm^3 acquiring voxel size, interpolated to 1x1x2 mm^3; reconstructed matrix 256x256; 70 slices; TE/TR 61/8500 ms; flip angle 90°; 32 gradient directions; no averages; max b-factor = 1000 s/mm^2;six minutes scan).

The tensor calculation of all images was performed using the ExploreDTI software (A. Leemans, University Medical Center, Utrecht, The Netherlands) and the fiber tractography through a deterministic methodology based onseeds strategies that enables to select the tract of interest.

Overview

Diffusion Tensor Image

Diffusion tensor image (DTI) is a Magnetic Resonance (MRI) technique which provides straightforward microstructural white matter (WM) information non-invasively, without using ionizing radiation or intravenous contrasts. The DTI analysis is based on the water diffusion patterns inside the axon tracts. The main theoretical concept in DTI measurements is based on the diffusion anisotropy of the water molecules. In brief, the water diffusion perpendicular to the fasciculus orientation is reduced, due to natural diffusion barriers (such as axon membranes and myelination), whereas it is relatively facilitated along the tract direction.[6] The measures of fractional anisotropy (FA) and diffusion values as mean Diffusivity (MD), axial diffusivity (AD-diffusivity in the tract direction) and radial diffusivity (RD-diffusivity perpendicular to the tract direction), can quantify and characterize the preferencial water molecules movement, allowing the assessment of the tract integrity. Additionally, the DTI-based fiber tractography allows to study WM through a visual 3D modeling that enables to virtually access fasciculli shapes while provides anatomical relevant regions of interest (ROI) that increase the analysis specificity.[7]

Temporal Stem

The temporal stem (TS) has a great topographic importance as this region can be a route of tumor, infection and seizure spread, and yet a surgical route to the mesial temporal region.[8,9]

Inconsistencies are found in the literature about the definition of TS, but it can be defined as a bridge of white matter between the temporal lobe and the basal ganglia, extending from the amygdala anteriorly to the level of the lateral geniculate body posteriorly. The temporal stem corresponds to the superior limit of the temporal horn and it is also related to the inferior limiting sulcus of insula superiorly. The length of the TS can be calculated from the limen insula anteriorly to the posterior insular point (intersection point of the Heschl gyrus with the inferior limiting sulcus of insula) posteriorly, and it measures about 33mm.[10] Thus, the TS can be arbitrarily divided on three portions. (Figure 1)

Although there are some inconsistencies about the fibers that compose the TS, the three main accepted components of the temporal stem are[5,8,11]:

1. The Uncinate Fasciculus (UF)
2. The Inferior Fronto-occipital Fasciculus (IFO)
3. The Meyer's Loop (ML)

Uncinate fasciculus

According to Kier et al, the fibers of the UF connect the cortical nuclei of the amygdala and the uncus with the subcallosal region, as well as they connect the temporal (superior, medium, inferior) gyri with the gyrus rectus, medial and lateral orbital gyri and the *pars orbitalis* of the inferior frontal gyrus. The isthmus or insular segment of the UF lies in the limen insula with a mean width and height of 7 and 5 mm respectively.[12] Türe et al. describes the UF as association fibers of the temporal and frontal lobes that pass through the limen insula and connect the fronto-orbital cortex to the temporal pole.[5,8,13]

The UF can be a pathway to seizure, tumor and infections spread, and its lesion is related to memory disturbances and schizophrenia symptoms.[13]

Several strategies can be used to find the UF fibers on DTI map and to reconstruct the tract. MATLAB platform was used with the NTA software, developed by the physicists of our neu-

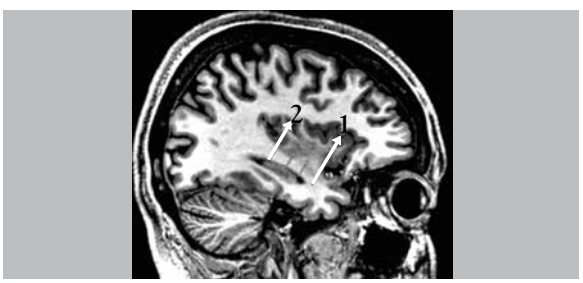

Figure 1. Temporal stem divided in three similar portions. 1) Limen insula; 2) Heschel gyrus.

roimaging laboratory. The regions of interest (ROIs) are chosen according to the tract to be analyzed.

For the uncinate fasciculus, the first ROIs ('seeds') can be placed in the coronal plane, encompassing all the temporal lobe, This ROIs are placed to 'seed', or to search for whatever fibers are coming through this specific region of the brain. Specifically, the coronal section can be placed at the same level of the anterior limit of the genu of the corpus callosum. From this anatomical reference, it is recommended to move the coronal section each five slices anteriorly or posteriorly in order to identify the temporal pole. Since this structure has been located, the ROIs can be added in the coronal plane in each five successive slices. After three first seeds were added, it is reasonable to draw the current tracts included before each subsequent seed is placed. The last ROI (seed) must be placed immediately anterior to the point where the UF assumes a parallel trajectory to the coronal plane. The second step is the placement of a ROI (in this case, an 'and) at the same coronal section of the most posterior 'seed', to make sure that the fibers travel mandatorily from the temporal to the frontal lobe, or from the frontal to the temporal lobe. The ROIs corresponding to the "most posterior seed" and the "and" must be adjacent and as close as possible, however without sobreposition, in order to ensure any fiber of UF were excluded. Due to individual anatomical variability, one more ROI ("and") can be added anteriorly in the frontal lobe (coronal section) if necessary to exclude fibers that does not belong to the UF. Alternatively, it is possible to exclude these fibers by adding a ROI ("not") on its trajectory. By following these steps, based on the anatomical description, the result is an image of the UF isolated in the brain. (Figure 2)

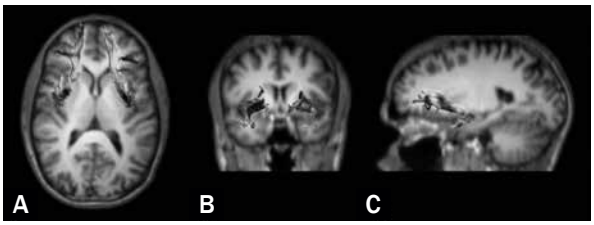

Figure 2. DTI-based fiber tractography of the uncinate fasciculus: A) Axial view; B) Coronal view; C) Sagittal view.

Inferior fronto-occipital fasciculus

The inferior fronto-occipital fasciculus is described as a long association fiber bundle that connects the frontal and occipital lobes and passes superiorly to the uncinate fasciculus inside the temporal stem.[5] *Kier* et al. has showed that the IFO extended from the level of the amygdala to the level of the posterior thalamus and the lateral geniculate body, and after exiting the temporal lobe trough the TS passed superior to the UF and into the extreme and external capsules.[8] Still in this study, their review suggests that the IFO is an unrecognized structure of the TS involved in some brain disorders such as postoperative cognitive impairment, posttraumatic syndromes, schizophrenia, Alzheimer disease. Martino et al. suggest that the IFO occupies the posterior two thirds of the TS, generally located about 10.9 mm (range from 8 to 15 mm) posteriorly to the limen insula at the inferior circular sulcus.[14]

Duffau et al. demonstrated, by direct electrostimulation, that the IFO is an important subcortical component of the semantic system and its disruption can lead to language disturbances.[15]

For the DTI imaging of the IFO, the first step is to place three ROIs ('seeds') in each three successive slices beginning anteriorly from the level of temporal pole, in the coronal view. The second step is to place one ROI ('and') in the occipital lobe in a coronal view,, at the level where the middle third of cerebellum can be identified, trying not to include upper parietal portions. This strategy makes sure that the fibers travel mandatorily from the frontal lobe to the occipital lobe, or vice versa. By following these steps, based on the anatomical description, the result is an image of the IFO isolated in the brain. (Figure 3)

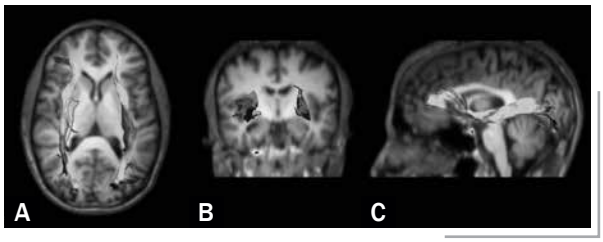

Figure 3. DTI-based fiber tractography of the inferior occiptofrontal fasciculus: A) Axial view; B) Coronal view; C) Sagittal view.

Some authors consider the IFO as bundle that also connects the frontal lobe with the posterior portion of both parietal and temporal lobes. In this case, the second step needs to be modified by placing the ROI (and) at the level of splenium of the corpus callosum (at the level of the anterior third of cerebellum). Using this strategy, the upper portion of the parietal lobe should be included by the ROI.

Optic radiations

The optic radiations after leaving the lateral geniculate body are divided into three main bundles (anterior, medium, posterior). ML is the anterior bundle of fibers of the optic radiations that start at the lateral geniculate body and course forward in the roof of the temporal horn of the lateral ventricle and then curves backward along the roof and lateral surface of the temporal horn and atrium. This anterior bundle is separated from the ventricle by the tapetum and ependima[16] Choi et al in their very illustrative work has shown that the distance from the limen insula to the anterior edge of the ML has ranged from 10.2–15.5 mm and that ML, in all the studied hemispheres, reaches the anterior extremity of the temporal horn.[17] The most common deficit from disruption of fibers from the ML is a superior homonymous quadrantanopia.[18]

For the fiber tracking of the optic radiations, the first ROIs ('seeds') can be placed on the axial view, starting from the lateral geniculate body. To ensure that the OR was circumscribed in all its craniocaudal extension, the 'seeds' must be added over five consecutive slices, and the middle one must be placed at the level of the anterior commissure. The second step is to place three exclusion ROIs ('nots'):one in the midsagittal section, another one in the axial plane at the level of the pons and the last one at the anterior limit of the temporal horn in the coronal plane. A third step can be performed by placing a ROI ('and') in the coronal view at the anterior portion of the occipital lobe to achieve a more accurate strategy. In group, these steps ensure (1) the exclusion of commissural, corticospinal and neighboring fibers, which does not belong to the OR and (2) the inclusion of fibers that connect the lateral geniculate body with the occipital cortex. The result is an image of the optic radiations isolated in the brain. (Figure 4)

Summarizing, the UF is located on the anterior third of the TS while the IFO and Meyer's Loop fibers are located in the two posterior thirds of the TS.

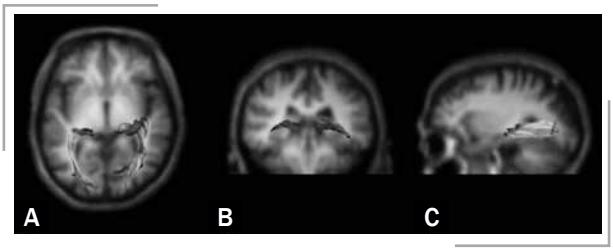

Figure 4. DTI-based fiber tractography of the optic radiations: A) Axial view; B) Coronal view; C)Sagittal view.

DISCUSSION

Several selective approaches to the mesial temporal region[4] were proposed without any clinical or surgical differences among them.[19]

With the advent of the DTI studies, great attention has been given to the white matter fiber tracts and its relation to epilepsy surgery. Because of its singular location, the TS components are under risk of damage by surgical treatment of TLE. As far as we know, the role of these TS fibers on seizure and neuropsychological outcomes are still matter of debate.

J. Peltier et al. has published an interesting review about the TS and its role in seizure spread and its functional significance. They stated that the TS seems to be the preferential pathway for seizure spread and that partial disruption of the UF can decrease the number and intensity of seizures.[13] Wieser et al. also stressed the importance of the UF disruption on the seizure control.[20]

On the other hand, Helmstaedter et al. has compared the transsylvian selective amygdalohippocampectomy (SAH) to the temporal pole resection (TPR) plus amygdalohippocampectomy, and has not found any difference on seizure control, but argued that the SAH was responsible for worst outcomes on verbal memory on the left side and TPR for worst outcomes on figure memory on the right side. The main hypothesis of the authors is that the SAH promoted more disruption of the TS than the TPR, leading to damage of the UF that connects the temporal lobe to the orbital frontal lobe. However, the authors have not analyzed the extent of TS disruption on the two different surgical techniques, neither the integrity of its white matter fiber tracts.[21]

Approaches as the transsylvian selective amygdalohippocampectomy (SAH) have been considered very selective in preserving the temporal neocortex, although it courses through the TS to access the temporal horn which leads to an important disruption of white matter fiber tracts. Concerning the risk of TS damage at the TLE surgery, elegant anatomical studies have been published. Sincoff et al and Choi et al have studied the transylvian approach and the fiber tracts that course inside the TS, and Peltier et al reviewed the microsurgical anatomy of the TS.[13,17,18] They showed that the UF and the ML are at great risk with the transylvian SAH approach, once the the istmus or insular segment of the UF lies in the limen insula with a mean width and height of 7 and 5 mm respectively and the distance from the limen insula to the anterior edge of the ML has ranged from 10.2–15.5 mm.

Lateral approaches to the mesial temporal lobe has the disadvantage of damaging neocortex and potential damage of the lateral and superior wall of the temporal horn, leading to lesion of the IFO and optic radiations.

Structural damage to the temporal stem through SAH and TPR approaches was studied by one of the authors (EG). Great damage to the TS was found on both approaches: 100% of patients submitted to the SAH approach had some degree of damage to the TS and 34,7% had damage that reached the posterior third of the TS; 100% of patients submitted to the TPR approach had some degree of damage to the TS and 52,9% had damage that reached the posterior third of the TS (not published data).

Concerning potential TS and neocortex protection, some anatomical reports proposed an anteromedial approach to the temporal horn to avoid injury to the optic radiation fibers and uncinate fasciculus.[17,22]

FINAL CONSIDERATIONS

The TS can be a pathway to seizure spread and can have an important role in cognitive disturbances. Until now, there is no evidence that preservation of the TS in epilepsy surgery can change patient's outcome or even influence seizure control and neuropsychological changes.

Anatomical knowledge and new neuroradiological MR sequences, such as DTI, can allow future studies accessing the TS status and its role on patient's outcome.

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LATE ONSET TEMPORAL LOBE EPILEPSY DUE TO CEREBRAL HYPOPERFUSION: CASE REPORT

EPILEPSIA DE LOBO TEMPORAL DE INÍCIO TARDIO DECORRENTE DE HIPOPERFUSÃO CEREBRAL: RELATO DE CASO

EPILEPSIA DE LÓBULO TEMPORAL DE INICIO TARDÍO DEBIDO A HIPOPERFUSIÓN CEREBRAL: RELATO DE CASO

Wendy Caroline de Souza Costa França[1], Ana Carolina Coan[1], Marcia E. Morita[1], Fernando Cendes[1]

ABSTRACT

Temporal lobe epilepsy is the most common form of focal epilepsy. The main pathological substrate of refractory TLE is hippocampal sclerosis (HS). HS has been associated with prolonged febrile and recurrent seizures. Other known causes for hippocampal injury are head trauma, ischemia, stroke and Alzheimer's disease. The exact causes of HS remain unknown, although they are probably diverse and multifactorial. The patient with TLE had no risk factors for epilepsy. His first seizure occurred immediately after an abdominal surgery complicated by profuse bleeding and hypotension during the procedure. The MRI showed hippocampal atrophy, probably due to hippocampal hypoperfusion, given the temporal relationship between the seizures and surgery. The etiology of hippocampal infarcts is discussed in this article. In a study with animal model, cerebral hypoperfusion led to a pattern of epileptiform activity similar to that found in the human hippocampus.

Keywords: Epilepsy, temporal lobe; Hippocampus; Atrophy; Ischemia; Sclerosis.

RESUMO

A epilepsia de lobo temporal (ELT) é a forma mais comum de epilepsia focal. O principal substrato patológico da ELT refratária é a esclerose hipocampal (EH). A EH tem sido associada a crises febris prolongadas e convulsões recorrentes. Outras causas conhecidas de dano hipocampal são: traumatismo cranioencefálico, isquemia, acidente vascular cerebral e doença de Alzheimer. As causas exatas da EH permanecem desconhecidas, apesar de serem provavelmente diversas e multifatoriais. O paciente com ELT não tinha fatores de risco de epilepsia. O paciente apresentou a primeira crise epiléptica no pós-operatório imediato de uma cirurgia abdominal complicada por sangramento profuso e hipotensão durante o procedimento. A RM evidenciou atrofia hipocampal, provavelmente decorrente da hipoperfusão hipocampal, dada a relação temporal das crises com o procedimento cirúrgico. A etiologia dos infartos hipocampais é abordada neste artigo. Em um estudo com modelo animal, o hipofluxo cerebral levou a um padrão de atividade epileptiforme semelhante ao encontrado no hipocampo humano.

Descritores: *Epilepsia de lobo temporal; Hipocampo; Atrofia; Isquemia; Esclerose.*

RESUMEN

La epilepsia de lóbulo temporal (ELT) es la forma más común de epilepsia focal. El principal sustrato patológico de la ELT refractaria es la esclerosis hipocampal (EH). La EH ha sido asociada a crisis febriles prolongadas y convulsiones recurrentes. Otras causas conocidas de daño hipocampal son: traumatismo craneoencefálico, isquemia, accidente vascular cerebral y enfermedad de Alzheimer. Las causas exactas de la EH permanecen desconocidas, a pesar de ser probablemente diversas y multifactoriales. El paciente con ELT no tenía factores de riesgo de epilepsia. El paciente presentó la primera crisis epiléptica en el postoperatorio inmediato de una cirugía abdominal complicada por sangrado profuso e hipotensión durante el procedimiento. La RM evidenció atrofia hipocampal, probablemente debido a la hipoperfusión hipocampal, dada la relación temporal de las crisis con el procedimiento quirúrgico. La etiología de los infartos hipocampales es abordada en este artículo. En un estudio con modelo animal, el hipoflujo cerebral llevó a un estándar de actividad epileptiforme semejante al encontrado en el hipocampo humano.

Descriptores: *Epilepsia de lóbulo temporal; Hipocampo; Atrofia; Isquemia; Esclerosis.*

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INTRODUCTION

Temporal lobe epilepsy

Temporal lobe epilepsy, especially mesial temporal lobe epilepsy (MTLE), is the most common form of focal epilepsy. The main pathological substrate in refractory MTLE is hippocampal sclerosis (HS).[1-3] The causes of HS remain unknown, although they are probably diverse and multifactorial.

One third of patient with TLE treated with antiepileptic drugs do not respond to medication.[4] In refractory cases, surgical treatment should be considered. Anterior temporal lobectomy is the most common surgery for epilepsy and is superior to drug treatment and other types of surgery in controlling seizures.[5, 6]

Hippocampal sclerosis

HS is a pathological finding observed for over 100 years with a specific pattern of neuronal loss in subregions of the hippocampal formation and other medial temporal structures.[7] HS has been associated with prolonged febrile[8-10] and recurrent seizures, but the relationship between repeated seizures and hippocampal atrophy is not well known.[11]

There are also other known causes of hippocampal injury such as head trauma, ischemia, stroke and Alzheimer's disease.[12]

Another etiology discussed in recent studies is hippocampal infarcts. When ischemia reaches large hippocampal areas it is associated with clinical symptoms of cognitive impairment or epilepsy. The susceptibility to ischemia found in this region, leading to neuronal degeneration, is influenced by risk factors that are not well known, but the size of the lesion is directly correlated with the clinical presentation.[13]

The excitotoxic damage related to seizure activity during the ischemia may also contribute to early injury of hippocampal neurons and can lead to dysfunction of extrahipppocampus regions too. In a animal model study, the occlusion of four-vessels led to a pattern of epileptiform activity similar to that found in human hippocampus, prefrontal and perirhinal cortex, areas that are also susceptible to ischemia.[14]

We describe in this case report a patient with no previous risk factors for TLE, who had his first seizure during the postoperative period, following a large abdominal surgery. MRI images showed signs of HS. We discuss here the possible mechanism that could be related to HS.

Case report (results)

We present a case of a 65 years old patient, male, who underwent an azygo-portal disconnection in September 2007 due to schistosomiasis associated with portal hypertension and esophageal varices. During surgery, the left gastric vein and artery, as well as, the esophagus varices and splenic artery were ligated. Splenectomy was not performed. Due to the presence of collateral circulation, patient presented profuse bleeding with hypotension during surgery, preventing cholecystectomy that was planned to be performed in the same surgical procedure.

After the operation, he developed episodes characterized by nonspecific malaise followed by loss of consciousness and right-handed automatisms, without postictal symptoms. These episodes recurred, occurring approximately seven times per month. In May 2013, there was an increase in seizure frequency to three times per week and 100 mg per day of phenobarbital was started. In November 2013, he was seen for the first time in our Epilepsy clinic. He complained of somnolence, without significant improvementin seizure control. Neurologic exam was normal. He had arterial hypertension and had no previous risk factors for epilepsy.

MRI was performed and showed bilateral hippocampal atrophy, more pronounced on left side, as well as, hyperintense signal in T2 and FLAIR images in the left amygdala and hippocampus. There was no abnormal hyperintensityin the right hippocampus. Inter-ictal EEG showed infrequent epileptiform activity and frequent slow waves in the left temporal region. carbamazepine was initiated and phenobarbital was slowly withdrawn. Patient was diagnosed with TLE and continues with an average of three focal dyscognitive seizures per day due to noncompliance.

DISCUSSION

This case describes a late-onset temporal lobe epilepsy,[15] with typical semiology, MRI and EEG features. In this case, there is a well-established temporal relationship between seizure onset and a major abdominal surgery with profuse bleeding and hypovolemia. Patient had no other risk factors for epilepsy, suggesting a causal relationship between the procedure and seizure onset.

In a study performed in rats, the model of four-vessels occlusion causing cerebral ischemia with monitoring by implanted electrodes in CA1, prefrontal and perirhinal cortex, identified reduced amplitude of alpha and occurrence of spikes during occlusion. During the first hours of reperfusion the majority of animals developed seizures.[14]As the mesial temporal lobe region is poorly irrigated, any significant reduction of blood flow in this area may cause an early ischemic injury, explaining the occurrence of seizures. We hypothesize that a similar mechanism might have occurred in the case reported herein. Due to profuse bleeding this patient probably became hypotense and presented brain hypoperfusion, leading to ischemia of the mesial temporal lobe structures. Therefore, as described in the animal model, the patient presented seizures during the first hours of reperfusion.

Hippocampal injury can lead to increased levels of neurogenesis and high concentration of neurotropic factors that appear to be beneficial in acute hippocampal dysfunction. However, in the chronic phase of injury, abnormal synaptogenesis and new neurons that arise in this area may lead to aberrant reorganization of synapses and progressive loss of GABAergic inhibition, generating sustained decline in neurogenesis and inflammation, which are deleteric and potentially epileptogenic.[12] The ongoing changes occurring overtime may explain the clinical deterioration of the patient after a few years of insult. Unfortunately, the patient had no neuroimaging studies prior to surgery in order to compare the hippocampus signal and volume. Investigation was not performed in the early postoperative period, which limits the etiological evaluation.

The literature shows that stem cells of the nervous system used in the early injured hippocampus in an animal models with minor injuries from toxic substances, brain trauma, and status epilepticus may have therapeutic value in preventing the development of temporal lobe epilepsy, depression and memory dysfunction. This can be attributed to potential mechanisms of functional recovery mediated by these cells[12] and represents hope for curative treatment for similar future cases.

FINAL CONSIDERATIONS

The correlation between temporal lobe epilepsy and hippocampal sclerosis is well established in the literature for over 100 years, however the causes of hippocampal sclerosis are not yet well defined. Studies with animal models as well as clinical follow-ups are essential to help us better understand this relationship. This knowledge would be important in the prevention of secondary MTLE and maybe in the development of more specific therapeutic options based on the mechanism of injury.

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LATE DIAGNOSIS OF LIMBIC ENCEPHALITIS ASSOCIATED WITH LGI1 ANTIBODIES LEADING TO RELAPSES

DIAGNÓSTICO TARDIO DE ENCEFALITE LÍMBICA ASSOCIADA A ANTICORPOS LGI1 QUE LEVAM A RECIDIVAS

DIAGNÓSTICO TARDÍO DE ENCEFALITIS LÍMBICA ASOCIADA A ANTICUERPOS LGI1 QUE LLEVAN A RECIDIVAS

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ABSTRACT

Autoimmune encephalitis has been a subject of research in the past few years; most of the cases are non-paraneoplastic and associated with an antibody to a surface protein of neurons. Studies have shown that VGKC complex is indeed represented by three proteins, and LGI1 is the most prevalent in limbic encephalitis. This entity is characterized by monophasic presentation with acute or subacute onset, memory loss, confusion, seizures and psychiatric symptoms. The presentation of anti-LGI1 antibodies in serum or CSF confirms the diagnosis. The treatment consists of immunotherapy with good clinical response, which is a criterion for diagnosis. We report a case of a patient with diagnosis confirmed six months after the symptoms onset, improvement after immunotherapy, but with episodes of relapse.

Keywords: Encephalitis/immunology; Limbic encephalitis; Inmunotherapy.

RESUMO

A encefalite autoimune tem sido assunto de pesquisa nos últimos anos, a maioria dos casos é não paraneoplásica e associada ao anticorpo para uma proteína de superfície dos neurônios. Estudos têm mostrado que o complexo VGKC é efetivamente representado por três proteínas, e a LGI1 é a mais prevalente na encefalite límbica. Essa entidade é caracterizada por apresentação monofásica com início agudo ou subagudo, perda de memória, confusão mental, crises convulsivas e sintomas psiquiátricos. A apresentação de anticorpos anti-LGI1 no soro ou no LCE confirma o diagnóstico. O tratamento consiste em imunoterapia com boa resposta clínica, que é um critério diagnóstico. Relatamos o caso de um paciente com diagnóstico confirmado seis meses após o início dos sintomas, com melhora após imunoterapia, porém com episódios de recaídas.

Descritores: *Encefalite/imunologia; Encefalite límbica; Imunoterapia.*

RESUMEN

La encefalitis autoinmune ha sido asunto de investigación en los últimos años; la mayoría de los casos es no paraneoplásica y asociada al anticuerpo para una proteína de superficie de las neuronas. Estudios han mostrado que el complejo VGKC es efectivamente representado por tres proteínas, y la LGI1 es la más prevalente en la encefalitis límbica. Esa entidad es caracterizada por presentación monofásica con inicio agudo o subagudo, pérdida de memoria, confusión mental, crisis convulsivas y síntomas psiquiátricos. La presentación de anticuerpos anti-LGI1 en el suero o en el LCE confirma el diagnóstico. El tratamiento consiste en inmunoterapia con buena respuesta clínica, que es un criterio diagnóstico. Relatamos el caso de un paciente con diagnóstico confirmado seis meses después del inicio de los síntomas, con mejora después de inmunoterapia, aunque con episodios de recaídas.

Descriptores: *Encefalitis/inmunología; Encefalitis límbica; Imunoterapia.*

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INTRODUCTION

Autoimmune encephalitis

Autoimmune encephalitis have been termed autoimmune channelopathies, despite the fact that the antigen is the protein surface and not the channel itself. These proteins can be found anywhere in the nervous system, but can be highly specific (eg limbic encephalitis). Although rare, the entity began to be recognized and treated in recent years, with the expectation of new antibodies discovery in the future.[1]

Affected patients have amnesia, confusion, seizures, psychiatric symptoms and some of them develop encephalopathy with movement disorders, loss of consciousness and hypothalamic disorders. Some patients have this condition related to tumors: ovarian teratoma, thymoma, small cells lung cancer; but the majority do not exhibit association with neoplasia.[1-3] Limbic encephalitis is an inflammatory process affecting predominantly the medial temporal lobe (hippocampus, amygdala) and orbitofrontal cortex. Patients typically present rapid progression of memory deficits, psychiatric disorders and seizure.[4] Autoimmune etiology must be considered if there are abnormalities on MRI, EEG and CSF, including antineuronal antibodies in serum and CSF.[5]

Limbic encephalitis: voltage gated potassium chanel spectrum (VGKC); leucine rich glioma inactivated 1 protein (LGI1)

Limbic encephalitis was initially described as a rare clinic pathological entity, involving amnesia, seizures and psychological disorders associated with neoplasia. However, paraneoplastic limbic encephalitis is a rare complication and a non-neoplastic type, associated with antibodies against neuronal proteins, began to be recognized recently. Several antibodies were identified in these cases, for example, anti-NMDAR, anti-AMPAR, anti-GABA BR type, anti-VGKC.[1]

Limbic encephalitis associated with antibodies to VGKC complex was the first one with well described response to immunotherapy.[3] Six main findings characterize these autoimmune responses: extracellular epitopes, binding of antibody and antigen is evident in affected cells, the antibody alters the structure or function of neuronal antigen, the effect of the antibody is usually reversible, the clinical presentation is similar to pharmacological or genetic models in which the antigen is disrupted, and the immune-mediated symptoms are responsive to immunotherapy in most cases.[6] Recent studies show antibodies to VGKC complex have affinity for other proteins identified in extracts of mammalian cortical neuronal membrane. The most common proteins are LGI1 and CASPER2, the less frequent is contactin 2.[1, 7]

Anti-LGI1 antibodies were initially identified by immunoprecipitation and spectroscopy, representing 70% of VGKC complex that was extracted from rabbit brain and identified using 125Ialfa – dendrotoxin, an ophidian toxin for VGKC subtypes Kv1.1, 1.2 and 1.6.[1]

LGI1 is a presynaptic protein associated with Kv1 VGKCs synaptic and other neuronal proteins. The two specific receptors for LGI1 are disintegrin and metalloproteinase domain-containing proteins 22:33 (ADAM22, 23), which is expressed post and presynaptically. It is also found in large quantities in the hippocampus and neocortex.[1] The probable physiopathology of limbic encephalitis anti-LGI1 is supported by the epileptogenic effects of purified IgG from a patient who has limbic encephalitis and anti-LGI1 causing neuronal excitability in hippocampus samples.[8]

Mutations in the gene that encondes the protein LGI1 are associated with autosomal dominant temporal lobe epilepsy, also defined as autosomal dominant lateral partial epilepsy with auditory aura.[6] In experiments using mices with transgenic expression of the protein, abnormal neurons were found and seizures occurred. Moreover, the protein deletion results in lethal phenotype characterized by myoclonic and tonic seizures.[9] Antibodies to LGI1 have been found mainly in patients with limbic encephalitis and epilepsy, but there are some cases with Morvan's syndrome.[1]

In a study conducted in the UK, high titers of antibodies to VGKC complex (> 400pmol by L - Normal: <100pmol per L) were found in 1-2 persons per million per year, and 67% of these patients had limbic encephalitis. The rest had neuromyotomia (11%), Morvan's syndrome (5%), isolated epilepsy (4%) or CSF findings that could not be fitted into any categoria.[1, 9] In another study in which the cohort was represented by a large number of paraneoplastic syndromes (51%), LGI1 were detected in 77% of the cases.[1]

This article aims to review the literature available on limbic encephalitis associated with antibodies to LGI1 and report an illustrative case, which is followed in our service.

MATERIAL AND METHODS

We performed an extensive investigation, including EEG, MRI, whole-body FDG-PET, and a full panel of auto-antibodies, including indirect immunofluorescence test for protein LGI1.

Case report (results)

Male patient, 64 years old, was found in his home during an episode of generalized tonic clonic seizure in June of 2013. The patient had a medical history of insulin-dependent diabetes refractory to treatment. At the emergency room, hyperglycemia was identified and reversed with insulin. After this episode, he began to present rapidly progressive dementia, with loss of recent memory, disorientation and later psychotic symptoms (aggression, irritability, persecutory thoughts). In January 2014, the patient was admitted for evaluation in our hospital. The family denied new episodes of seizures but reported episodes of exacerbation of the other symptoms described above. General physical exam was normal. On neurological exam, he was disoriented in time and space and he had difficulties in the exam of recent memory (recall); he also had symmetric diminished vibratory sensitivity in both legs up to the knees and bilateral intentional tremor. On further investigation, MRI showed mild atrophy of the hippocampi, more pronounced on the left. Three routine EEGs performed on occasion demonstrated no changes. CSF presented increase of IgG (10.5mg/dl) and protein (84mg/dl). He scored 14/30 on MOCA (Montreal Cognitive Assessment) (visual space and executive function 3/5, naming 3/3, attention 5/6, language 0/3, abstraction 0/2, recall 0/5, orientation 3/6). Whole-body PET and oncology antibodies were negative. Indirect immunofluorescence test for protein LGI1 was positive in blood and in CSF. The patients received intravenous immunoglobulin with improvement of the symptoms (MOCA after-visual space and executive function 5/5, naming 3/3, attention 5/6, language 2/3, abstraction 2/2, recall 1/5, orientation 4/6-22/30). He was discharged with prednisone 60 mg per day and orientation to decrease the dose slowly, carbamazepine 200 mg three times daily and maintenance of insulin. In February 2014, the patient returns to the emergency due to a status epilepticus. After seizure control, further investigation showed worsening of the CSF pattern

(white cells 13 red cells 52 proteins 309 IgG 47,5 glucose 223) and he underwent a pulse therapy with methylprednisolone 1 g daily for 3 days, with improvement of the symptoms. In March 2014, he returned to the hospital due to progressive worsening of the periods of fluctuations of humor (threatened his son, ran away from home), which improved after plasmapheresis. In April 2014, he came back to the hospital because of viral diarrhea and decompensation of diabetes, periods of mood fluctuation and disorientation. New cycle of immunoglobulin was prescribed and he remains as an outpatient in our epilepsy clinic. As future therapy, we decided to maintain treatment with cyclophosphamide and repeated plasmapheresis in order to avoid new relapses.

DISCUSSION

Clinical presentation

Patients with anti-LGI1 enchephalitis present acute or subacute onset, memory loss, confusion, seizures, agitation and psychiatric symptoms for days or weeks. There may be a history of infection. Some patients presented in the onset psychosis episode[10] or cryptogenic epilepsy.[11] Most common after 40 years of age and in men (2:1).[1] In the case reported above, the patient initially presented with secondary generalized seizure that was attributed to hyperglycemia, followed by loss of recent memory, exacerbation episodes with confusion and agitation.

REM sleep behavior disorder is commom,[12] other sleep disorders , startle syndrome,[13] ataxia and hypothermia in some cases.[14] Intestinal pseudo-obstruction can also be found, probably due to the action of antibodies in myenteric plexus.[15]

Patients may present brief dystonic movements, mainly of the face and upper extremities, which is called brachiofacial dystonic seizure, progressing to symptoms of encephalitis.[16,17] In some cases, these movements may occur 60-100 times per day and can be misdiagnosed as myoclonus or startle disease.[16]

Investigation

Serum sodium: Low concentrations of sodium (115-130mmol per L) before the start of antiepileptic drugs or any other treatment has been a clue to the diagnosis of limbic encephalitis associated with antibodies against the VGKC complex.[18] In a study conducted in the United States, 60% of the patients experienced hyponatremia, which can be related to syndrome of inappropriate secretion of antidiuretic hormone by the LGI1 expression in the hypothalamus and kidney.[9] Unfortunately, we do not have this information about our patient.

Antibody to LGI1: In patients who have limbic encephalitis, levels are normally high (> 400 pmol/L) and it can be higher than 1000 pmol/L. The test conducted was qualitative and patient was positive in blood and CSF. However, low titers can be found, especially in children[19, 20] in the recovery period or in patients who improved espontaneously.[21] In addition, lower titers are found in patients who have epilepsy, in elderly patients[22] and neoplastic patients, particularly those with timoma[23, 24] or lung and others carcinomas.[24-26]

Neoplastic screening: Although most cases of autoimmune encephalitis anti LGI1 are unrelated to cancer, it is important to exclude this possibility. Thymoma is the most common tumor related to this limbic encephalitis[1]. Oncogenic antibodies, whole body PET and CT thoraco-abdominal presented no evidence of cancer in the case reported.

Magnetic resonance image (MRI): T2 or FLAIR hyperintense signal in unilateral or bilateral mesial temporal lobe is common, as described in our patient. However, 45% of patients with limbic encephalitis with anti LGI1 have a normal MRI at the beginning or during the course of disease.[16]The amygdala is affected in some cases, even without changes in temporal lobe.[27,28] Despite the treatment and fluctuation of symptoms presented by the patient, there was no significant change in the follow-up MRI.

PET: PET may be more sensitive than MRI to assess hippocampal dysfunction. It shows hypermetabolism in the early stage of the disease and hypometabolism in later stages.[27, 28]

Electroencephalogram (EEG): The EEG shows interictal foci of epileptiform activity or slow activity in the anterior and mesial temporal region, it may also be detected in the frontal region, as well as ictal activity in the same areas.[1] For brachiofacial dystonia, electrodecrement may precede events, which is typical of tonic seizures.[6] During hospitalization, our patient showed no seizures and his EEG was normal.

Cerebrospinal fluid (CSF): IgG and oligloconal bands (OCB) can help identify an autoimmune change, as in our patient, before confirmation by antibodies. However, OCB cannot be detected early in the disease and even during its evolution.[18, 29]

Classification and pathogenesis

Vincent et al. brings important questions in their review on the subject discussed above, for example, questions such as how these diseases are classified - based on clinical presentation or in antibody? Whereas it is still restricted the access to antibodies, perhaps the clinical classification prevails until the tests are commercially more accessible to institutions with less purchasing power. Furthermore, the therapeutic procedure is the same, regardless of the antibody that is causing, and the importance of this fact lies in the better understanding of the physiopathology, in response to immunotherapy and prognosis of the condition.

Most cases of autoimmune encephalitis associated with anti - LGI1 are not related to cancer, and the mechanism leading to the production of these antibodies is unknown. In the case reported above, patient had refractory diabetes, but the test for anti –GAD antibodies was negative.

Diagnosis

Antibodies are identified by indirect immunohistochemistry. Immunopreciptation of protein extracts of neurons and subsequent spectroscopy can identify the antigen. For this, the patient serum is used, which contains the basal cells to be analyzed. The radioimmunoassay has become commercially avaliable.[1] Antibody concentrations are generally higher in serum than in CSF, which could be negative.[22, 25] The test available at our institution, is the indirect immunofluorescence in HEK293 cells transinfected with the LGI1 protein gene.

Definitive diagnosis is characterized by the presence of specific antibody in serum or CSF and responding to immunotherapy. Probable diagnosis is defined by the presence of antibody or presence of another neuronal marker of immune process discussed above or a related clinical finding, and response to immunotherapy. Possible diagnosis is described as a clinical diagnosis, and other neuronal marker of immune process (anti - GAD antibodies of unknown neuronal surface) or response to immunotherapy.[30] Our patient had a late diagnosis, six months after symptoms onset, and obtained response to immunotherapy, but he showed relapse of the condition after 3 weeks. The same occurred with other therapeutic options used.

Differential diagnosis

Other diagnoses should be considered in clinical conditions like this: Wernick's encephalopathy, encephalopathy induced by drugs or toxins, and viral encephalitis. Under the relatively recent knowledge of these antibodies, the question about the diagnosis arises on similar cases that have been diagnosed in the past as unproved viral encephalitis. In a study of encephalitis in the UK, 3% of patients had antibodies against complex VGKC.[31]

Studies in non-prion rapidly progressive dementia have found anti VGKC complex antibody, even in patients who fit in the criteria including for Creutzfed-Jakob disease with good response to immunotherapy.[32]

Treatment

The role of antibodies in neuromuscular diseases is well known since the 1970s. Affected patients have rapid improvement with plasma exchange, which removes antibodies from the circulation. Over the past 10 years, various diseases of the central nervous system, mediated by antibodies against surface proteins expressed in neurons, with significant improvement after immunotherapies have been discovered, although the recovery is slower compared to the peripheral diseases.[1]

This slow improvement could be due to a long time needed to recover the CSF changes and slow reduction of antibodies concentration.[1] In addition, the improvement after plasmapheresis is discussed, since the probable pathophysiology of these encephalitis involves intrathecal production of antibodies. The use of cyclophosphamide and rituximab are also debatable, but with few case reports referring good response.[33]

Some studies indicate the use of intravenous immunoglobulin, associated or not with plasmapheresis, followed by high doses of oral corticosteroids. For those who do not respond to first-line treatment and have negative screening for cancer, second-line immunotherapy with rituximab, cyclophosphamide, or both should be used.[30] There are no studies about prolonged immunotherapy to prevent relapse, and there is not known correlation between a high risk of relapse in patients who were not properly treated in the first event.[34] However, it was clear, in our experience with this case, the refractoriness after a delayed treatment, even using first-line drugs, such as described in the literature. As described above, after intravenous immunoglobulin, pulse steroids, plasmapheresis and new cycle of immunoglobulin, we opted for the use of cyclophosphamide and plasma exchange in case of exacerbations, which have been frequent in this patient.

Focal or generalized seizures related to LGI1 encephalitis do not respond well to anti-epileptic drugs; however, respond to immunotherapy such as steroids, plasmapheresis and intravenous immunoglobulin.[16, 18, 22] This was experienced by our team in conducting this case.[18]

Follow-up and Prognosis

Non-neoplastic immune-mediated limbic encephalitis has a better prognosis than paraneoplastic limbic encephalitis.[1] The majority responds to treatment in weeks.[30] However, the prognosis is unclear in cases with late diagnosis.

Serum sodium returns to normal and anti-LGI1 antibodies become undetectable within a few months after the start of treatment, increasing the hypothesis of a monophasic illness in many patients. A small number of patients may present with persistently detectable serum antibodies or reappearance of the same level, showing slow improvement clinically or relapse.[16,22] The need to repeat the following antibodies is questionable because the true utility is unknown.[1]

FINAL CONSIDERATIONS

Limbic encephalitis associated with anti-LGI1, as well as other encephalitis associated with antibodies against neuronal surface proteins, needs further studies on is pathophysiology in order to improve the understanding of the course of the disease and to provide better treatment.

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CONTRAINDICAÇÃO: em casos de hipersensibilidade ao princípio ativo (lacosamida) ou a qualquer um dos excipientes.
INTERAÇÃO MEDICAMENTOSA: medicamentos conhecidos por prolongar o intervalo PR e antiarrítmicos classe I.

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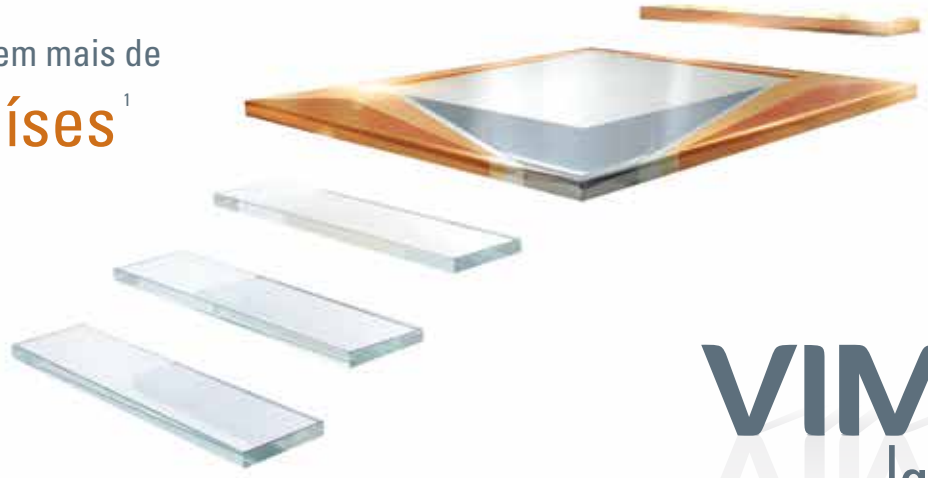

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